



REC'D 08 SEP 2004

WIPO

PCT

# Kongeriget Danmark

Patent application No.: PA 2003 01175

Date of filing: 15 August 2003

Applicant:  
(Name and address) H. Lundbeck A/S  
Ottiliavej 9  
DK-2500 Valby  
Denmark

Title: A method and an arrangement for advertising or promoting

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

**PRIORITY DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH  
RULE 17.1(a) OR (b)

Patent- og Varemærkestyrelsen  
Økonomi- og Erhvervsministeriet

06 September 2004

Pia Høybye-Olsen



15 AUG. 2003

437 DK

1

Modtaget

# CYCLOPROPYL DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS

## FIELD OF THE INVENTION

The present invention relates to novel compounds which are NK3 receptor antagonists and  
5 as such useful for treatment of diseases where the NK3 receptor is implicated.

## BACKGROUND OF THE INVENTION

Three tachykinins, Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are  
widely distributed throughout the peripheral and central nervous systems. The biological  
10 effects of these neuropeptides are primary mediated via binding to and subsequent  
activation of the three neurokinin receptors, NK1, NK2 and NK3. Substance P is considered  
to be the endogenous ligand for the NK1 receptor and likewise NKA and NKB for the NK2  
and NK3 receptors, respectively. However, recent data indicates that there exist cross-  
reactivity within the tachykinin system, which might be of physiological relevance as both  
15 NKA and NKB potentially are able to bind and activate the NK1 receptor (for review see  
Maggi, CA et al: Trends Pharmacol Sci. 1997, 18, p351-5). The three receptor subtypes  
belong to the G-protein-coupled receptor super family and have been cloned in various  
species including mice, rats and humans (Nakanishi S: Annu Rev Neurosci. 1991, 14, p123-  
36).

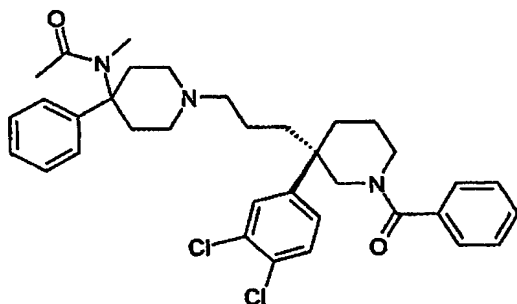
20

The three tachykinin receptors are expressed both centrally and in the periphery. The NK3  
receptor is mainly expressed centrally in regions including cortex, striatum, substantia nigra  
compacta, ventral tegmental area, hypothalamus, amygdala and hippocampus (Stoessl AJ  
et al: Brain Res. 1990, 534, p1-7, Koutcherov Y et al: Neuroreport. 2000, 11, p3127-31). In  
25 the periphery, the NK3 receptor is expressed in regions including colon, kidney, lungs and  
the urinary bladder (Regoli D et al: Trends Pharmacol Sci. 1988 Aug;9(8): 290-5)( Kamal i  
F: Curr Opin Investig Drugs. 2001 Jul;2(7):950-6). Centrally, the NK3 receptor is expressed  
on cholinergic (Chen LW et al: Neuroscience. 2001;103(2):413-22), noradrenergic  
(references within Oury-Donat F et al: J Pharmacol Exp Ther. 1995, 274, p148-54) and  
30 dopaminergic neurons (Keegan KD et al: Br. J. Pharmacol. 1992, 105, p3-5). In agreement  
with these results, activation of the NK3 receptor has been reported to be implicated in the  
regulation of various monoamine transmitters, e.g. dopamine and acetylcholine (Marco N et  
al: Neuropeptides. 1998, 32, p481-8, Stoessl AJ et al: Brain Res. 1990, 517, p111-6),

noradrenaline (Jung M et al: Neuroscience. 1996, 74, p403-14) and serotonin (Stoessl AJ et al: Brain Res. 1990, 517, p111-6).

The NK3 receptor-mediated regulation of monoamine systems support that the NK3  
5 receptor is involved in diverse functions including memory, learning, cortical processing  
and behavioral control (Yip J et al: Br J Pharmacol. 1997, 122, p715-25, Ding YQ et al: J  
Comp Neurol. 1996, 364, p290-310, Mileusnic D et al: Neurobiol Aging. 1999, 20, p19-35)  
and that it is target for various psychological and neurological disorders (Emonds-Alt X et  
al: Can J Physiol Pharmacol. 2002, 80, p482-8, Kamali F, Curr Opin Investig Drugs. 2001,  
10 2, p950-6, Langlois X et al: J Pharmacol Exp Ther. 2001, 299, p712-7). Indeed, the NK3  
receptor has been reported to be implicated in modulation of anxiety (Ribeiro SJ et al:  
Neuropeptides. 1999, 33, p181-8).

Further, it has been reported that the NK3 receptor antagonist SR142801 has effect against  
15 schizophrenia, in particular positives symptoms. SR142801 is described in, e.g., EP 673928.  
The structure of SR142801 is outlined below (Kamali F: Curr Opin Investig Drugs. 2001,  
Jul;2(7):950-6).



In vivo, NK3 receptor activation centrally has been reported to mediate hypertension and  
20 tachycardia (Nagashima A et al: Brain Res. 487, 1989, p392-396, Takano Y et al: Brain  
Res. 1990, 528, p231-7, Picard P et al: Br J Pharmacol. 1994, 112, p240-9) whereas NK3  
receptor activation in the periphery mediates hypotension and bradycardia (Couture R et al:  
Naunyn Schmiedebergs Arch Pharmacol. 1989, 340, p547-57). Additional in vivo studies  
have indicated that NK3 receptor activation decrease water, salt and alcohol intake (Massi  
25 M et al: Brain Res Bull. 1991 26 p155-60, Massi M et al: Neurosci Lett. 1988, 92, p341-6  
and Ciccocioppo R et al: Brain Res Bull. 1994, 33, p71-7) which together with the  
localization of the NK3 receptor on MCH neurons support a role of the NK3 receptor in the

regulation of food intake (Griffond B et al: *J Chem Neuroanat.* 1997, 12, p183-9). Further in vivo studies have shown that the NK3 receptor is implicated in renal control of water and electrolyte homeostasis (Yuan YD: *Br J Pharmacol.* 1997, 120, p785-96). Activation of the NK3 receptor has been reported to inhibit gastric acid secretion (Improta G et al: *Peptides.* 1991, 12, p1433-4), induce oral dyskinesia (Liminga U et al: *Pharmacol Biochem Behav.* 1991, 38, p617-20) and oedema (Inoue H et al: *Inflamm Res.* 1996, 45, p316-23).

In vitro NK3 activation has been reported to have proconvulsive effect (Maubach KA et al: *Neuroscience.* 1998, 83, p1047-62) and to mediate hyperexcitability in ischemic injury (Stumm R et al: *J Neurosci.* 2001, 21, p798-811).

Selective high affinity non-peptide NK3 receptor antagonists have been shown to be antinociceptive (Fioramonti J et al: *Neurogastroenterol Motil.* 2003, 15, p363-9, Couture R et al: *Life Sci.* 2000, 66, p51-65, Julia V et al: *Gastroenterology.* 1999, 116, p1124-31, Coudore-Civiale MA: *European Journal of Pharmacology* 1998, 361, p175-184) and analgesic (Houghton AK et al: *Neuropharmacology.* 2000, 39, p133-40). In addition, studies demonstrate consistent effect of a NK3 receptor antagonist against visceral pain encouragingly precluding constipation (Mayer EA et al: *Gastroenterology.* 1999, 116, p1250-2, Julia V et al: *Gastroenterology.* 1999 116 p1124-31) Similarly inhibition of the NK3 receptor prevent gut inflammation highlighting effect against inflammatory bowel disease (Mazelin L et al: *Life Sci.* 1998, 63, p293-304), cough, airway hyperresponsiveness, microvascular hypersensitivity and reduction of bronchoconstriction (Daoui S et al: *Am J Respir Crit Care Med.* 1998, 158, p42-8, Rumsey WL et al: *J Pharmacol Exp Ther.* 2001, 298, p307-15, Daoui S et al: *Pulm Pharmacol Ther.* 1997 10 p261-70). Inhibition of the NK3 receptor as therapeutic strategy for Parkinsons disease has been substantiated in several reports (Arenas E: *J Neurosci.* 1991, 11, p2332-8, Kemel ML et al: *J Neurosci.* 2002, 22, p1929-36).

Pre-clinical, in vivo and in vitro studies support that NK3 receptor antagonists are of relevance for the treatment or prevention of various disorders including: schizophrenia, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation,

inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema and plasma extravasation.

Hence, there is a desire for NK3 receptor antagonists. The present inventors have now found  
5 such compounds with a strong affinity for the NK3 receptor.

Several patent applications relates to compounds disclosed as NK receptor antagonist, e.g. EP 474561, EP 512901 and WO 03/051869. In particular, some patent applications relates to compounds disclosed as NK3 receptor antagonist, e.g. WO 9710211, US 5434158 and EP  
10 673928. US 5750549 disclose cyclopentane derivatives as NK1 receptor antagonist.

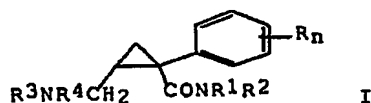
The compounds of the present invention are all cyclopropyl derivates. As indicated in the following some patent applications relates to different cyclopropane derivatives. Non of these patent application relates to the NK3 receptor or others of the NK receptors.

15 JP 03056415 describes cyclopropane derivatives of the following formula



for treatment of cerebral ischemia.

20 EP 68999 describes cyclopropane derivatives of the following formula



for treatment of depression.

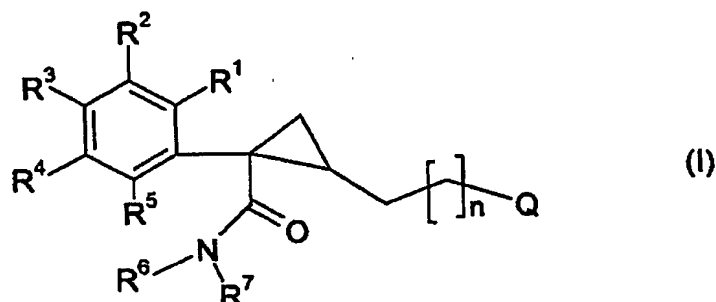
25

## SUMMARY OF THE INVENTION

The objective of the present invention is to provide compounds that are antagonists at the NK3 receptor. Some of the compounds may also have affinity for the NK1 and/or NK2 receptor.

30

Accordingly, in one aspect the present invention relates to a compound having the general formula I:



5

wherein the substituents are as defined herein, or a salt thereof, in particular a pharmaceutically acceptable acid addition salt thereof. The invention in particular provides the (1S,2R)-isomer of such compounds.

10 Moreover, the invention provides a pharmaceutical composition comprising a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof. Accordingly, the invention provides a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof for use in medicine.

15 The invention also provides the use of a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of: schizophrenia, psychosis, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation,  
 20 inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema and plasma extravasation.

Further, the invention also provides a method for the treatment of diseases selected from the group consisting of: schizophrenia, psychosis, depression, anxiety, Parkinson's disease,  
 25 pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema and

plasma extravasation, comprising administering a therapeutically effective amount of a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof.

## DETAILED DESCRIPTION OF THE INVENTION

5

### Definitions

The term "halogen" means fluoro, chloro, bromo or iodo.

- 10 The expression "C<sub>1-6</sub>-alk(en/yn)yl" means a C<sub>1-6</sub>-alkyl, a C<sub>2-6</sub>-alkenyl or a C<sub>2-6</sub>-alkynyl group.

The term "C<sub>1-6</sub> alkyl" refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

The term "C<sub>2-6</sub> alkenyl" designate such groups having from two to six carbon atoms, including one double bond, including but not limited to ethenyl, propenyl, and butenyl.

- 20 The term "C<sub>2-6</sub> alkynyl" designate such groups having from two to six carbon atoms, including one triple bond, including but not limited to ethynyl, propynyl and butynyl.

The expression "C<sub>3-8</sub>-cycloalk(en)yl" means a C<sub>3-8</sub>-cycloalkyl or a C<sub>3-8</sub>-cycloalkenyl group.

- 25 The term "C<sub>3-8</sub>-cycloalkyl" designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term "C<sub>3-8</sub>-cycloalkenyl" designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and one double bond, including but not limited to cyclopropenyl, cyclopentenyl, cyclohexenyl, etc.

30

In the expression "C<sub>3-8</sub>-cycloalk(en)yl-C<sub>1-6</sub>-alk(en/yn)yl", the terms "C<sub>3-8</sub>-cycloalk(en)yl" and "C<sub>1-6</sub>-alk(en/yn)yl" are as defined above.

The term "C<sub>1-6</sub>-alk(en/yn)oxy" refers to groups of the formula C<sub>1-6</sub>-alk(en/yn)yl-O-, wherein C<sub>1-6</sub>-alk(en/yn)yl are as defined above.

- 5 The terms "C<sub>1-6</sub>-alk(en/yn)yl-carbonyl", "C<sub>1-6</sub>-alk(en/yn)yl-aminocarbonyl" and "di-(C<sub>1-6</sub>-alkyl)aminocarbonyl" refers to groups of formula C<sub>1-6</sub>-alk(en/yn)yl-CO-, C<sub>1-6</sub>-alk(en/yn)yl-NH-CO- and (C<sub>1-6</sub>-alk(en/yn)yl)<sub>2</sub>-N-CO-, respectively, wherein C<sub>1-6</sub>-alk(en/yn)yl are as defined above.
- 10 In the expressions "C<sub>1-6</sub>-alk(en/yn)yl-amino", "di-(C<sub>1-6</sub>-alkyl)amino", "C<sub>1-6</sub>-alk(en/yn)ylthio", "halo-C<sub>1-6</sub>-alk(en/yn)yl", "halo-C<sub>1-6</sub>-alk(en/yn)yl-sulfonyl", "halo-C<sub>1-6</sub>-alk(en/yn)yl-sulfanyl", "C<sub>1-6</sub>-alk(en/yn)ylsulfonyl", and "C<sub>1-6</sub>-alk(en/yn)ylsulfanyl" etc., the terms "C<sub>1-6</sub>-alk(en/yn)yl" and "halo" are as defined above.
- 15 As used herein, the term "acyl" refers to formyl, C<sub>1-6</sub>-alk(en/yn)ylcarbonyl, arylcarbonyl, aryl-C<sub>1-6</sub>-alk(en/yn)ylcarbonyl, C<sub>3-8</sub>-cycloalk(en)ylcarbonyl or a C<sub>3-8</sub>-cycloalk(en)yl-C<sub>1-6</sub>-alk(en/yn)yl-carbonyl group, wherein C<sub>1-6</sub>-alk(en/yn) and C<sub>3-8</sub>-cycloalk(en)yl is as defined above and aryl is as defined below.
- 20 The term "thioacyl" is the corresponding acyl group, in which the carbonyl group is replaced with a thiocarbonyl group.

The term "aryl" refers to a carbocyclic aromatic group, such as phenyl or naphthyl, in particular phenyl and includes both substituted or unsubstituted carbocyclic aromatic groups. Thus, the aryl is optionally substituted with one or more substituents selected from the substituent list as defined below. Accordingly, the term aryl as used herein means an optionally substituted carbocyclic aromatic group, e.g. phenyl or naphthyl, such that said aromatic group is substituted with one ore more substituents selected from the substituent list defined below, e.g., C<sub>1-6</sub>-alkyl or halogen. The aryl is preferably mono- or bicyclic.

30

The term "heteroaryl" refers to an aromatic group containing at least one carbon atom and one or more heteroatoms selected from O, S or N. As used herein the term "heteroaryl" refers to a mono- or bicyclic heterocyclic group including but not limited to indolyl, thienyl,



pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzofuranyl, benzothienyl, pyridyl and furanyl, in particular pyrimidyl, indolyl, and thienyl. The term heteroaryl as used herein includes both substituted or unsubstituted heteroaryl. Thus, the heteroaryl is optionally substituted with one or more substituents selected from the  
5 substituent list as defined below, e.g., C<sub>1-6</sub>-alkyl or halogen.

The term "monocyclic heteroaryl" as used herein refers to 5- to 6- membered aromatic systems containing 1 to 5 carbon atoms and one or more heteroatoms selected from O, S or N.

10

Accordingly, the term "heteroaryl" refers to 5-membered monocyclic rings such as, but not limited to, 1*H*-tetrazolyl, 3*H*-1,2,3-oxathiazolyl, 3*H*-1,2,4-oxathiazolyl, 3*H*-1,2,5-oxathiazolyl, 1,3,2-oxathiazolyl, 1,3,4-oxathiazolyl, 1,4,2-oxathiazolyl, 3*H*-1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,4,2-dioxazolyl, 3*H*-1,2,3-dithiazolyl, 3*H*-1,2,4-dithiazolyl,  
15 1,3,2-dithiazolyl, 1,4,2-dithiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1*H*-imidazolyl, 1*H*-pyrazolyl, 1*H*-pyrrolyl, furanyl, thienyl, 1*H*-pentazole.

20 Further, the term "heteroaryl" refers to 6-membered monocyclic rings such as, but not limited to, 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, 4*H*-1,3,5-oxathiazinyl, 1,4,2-oxathiazinyl, 1,4,3-oxathiazinyl, 1,2,3-dioxazinyl, 1,2,4-dioxazinyl, 4*H*-1,3,2-dioxazinyl, 4*H*-1,3,5-dioxazinyl, 1,4,2-dioxazinyl, 2*H*-1,5,2-dioxazinyl, 1,2,3-dithiazinyl, 1,2,4-dithiazinyl, 4*H*-1,3,2-dithiazinyl, 4*H*-1,3,5-dithiazinyl, 1,4,2-dithiazinyl, 2*H*-1,5,2-dithiazinyl, 2*H*-1,2,3-oxadiazinyl, 2*H*-1,2,4-oxadiazinyl, 2*H*-1,2,5-oxadiazinyl, 2*H*-1,2,6-oxadiazinyl, 2*H*-1,3,4-oxadiazinyl, 2*H*-1,3,5-oxadiazinyl, 2*H*-1,2,3-thiadiazinyl, 2*H*-1,2,4-thiadiazinyl, 2*H*-1,2,5-thiadiazinyl, 2*H*-1,2,6-thiadiazinyl, 2*H*-1,3,4-thiadiazinyl, 2*H*-1,3,5-thiadiazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 2*H*-1,2-oxazinyl, 2*H*-1,3-oxazinyl, 2*H*-1,4-oxazinyl, 2*H*-1,2-thiazinyl, 2*H*-1,3-thiazinyl, 2*H*-1,4-thiazinyl, pyrazinyl,  
25 30 pyridazinyl, pyrimidyl, pyridyl, 2*H*-pyranyl, 2*H*-thiinyll.

Finally the term "heteroaryl" also refers to bicyclic rings such as, but not limited to, 3*H*-1,2,3-benzoxathiazolyl, 1,3,2-benzodioxazolyl, 3*H*-1,2,3-benzodithiazolyl, 1,3,2-

benzodithiazolyl, benzfurazanyl, 1,2,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, 1*H*-benzotriazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzothiazolyl, 1*H*-benzimidazolyl, 1*H*-indazolyl, 3*H*-1,2-benzoxathieryl, 1,3-benzoxathieryl, 3*H*-2,1-benzoxathieryl, 3*H*-1,2-benzodioxolyl, 1,3-benzodioxolyl 3*H*-1,2-benzodithieryl, 1,3-benzodithieryl, 1*H*-indolyl, 2*H*-isoindolyl, benzofuranyl, isobenzofuranyl, 1-benzothienyl, 2-benzothienyl, 1*H*-2,1-benzoxazinyl, 1*H*-2,3-benzoxazinyl, 2*H*-1,2-benzoxazinyl, 2*H*-1,3-benzoxazinyl, 2*H*-1,4-benzoxazinyl, 2*H*-3,1-benzoxazinyl, 1*H*-2,1-benzothiazinyl, 1*H*-2,3-benzothiazinyl, 2*H*-1,2-benzothiazinyl, 2*H*-1,3-benzothiazinyl, 2*H*-1,4-benzothiazinyl, 2*H*-3,1-benzothiazinyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, isoquinolyl, quinolyl, 1*H*-2-benzopyranyl, 2*H*-1-benzopyranyl, 1*H*-2-benzothiopyranyl or 2*H*-1-benzothiopyranyl.

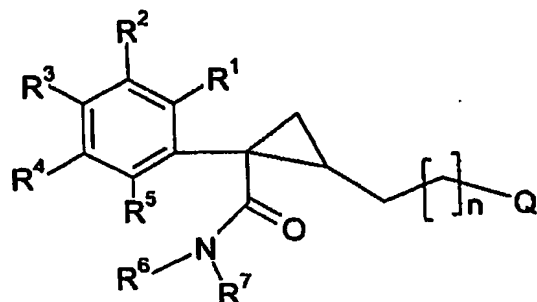
The expression "substituent list" means substituents selected from the group consisting of:  
 15 halogen, cyano, nitro, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)amino, C<sub>1-6</sub>-alkylcarbonyl, aminocarbonyl, C<sub>1-6</sub>-alkylaminocarbonyl, di-(C<sub>1-6</sub>-alkyl)aminocarbonyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkylthio, alkylsulphonyl, hydroxy, trifluoromethyl, trifluoromethylsulfonyl, C<sub>1-6</sub>-alkylcarbonylamino and C<sub>1-6</sub>-alkylcarbonylC<sub>1-6</sub>-alkylamino".

20 The term "treatment" as used herein in connection with a disease or disorders includes also prevention as the case may be.

#### **Compounds of the invention and salts thereof**

The present invention relates to compounds of formula I which are antagonists at the NK3  
 25 receptor. These products may therefore be useful in the treatment of certain diseases such as schizophrenia, psychosis, depression, anxiety, or Parkinson's disease, in particular schizophrenia.

In one aspect, the invention relates to compounds of formula I,



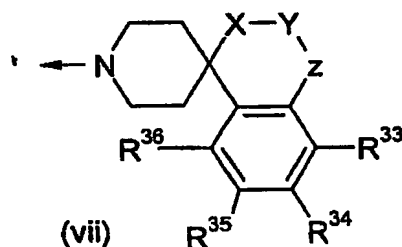
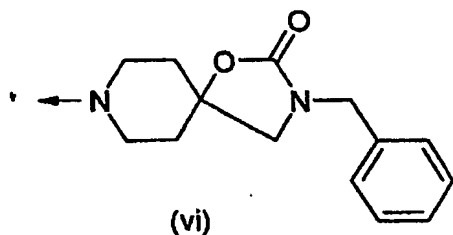
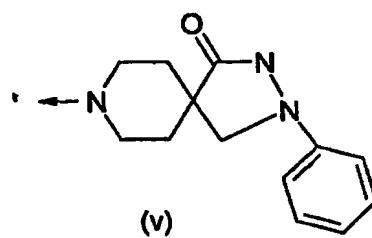
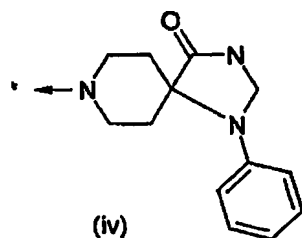
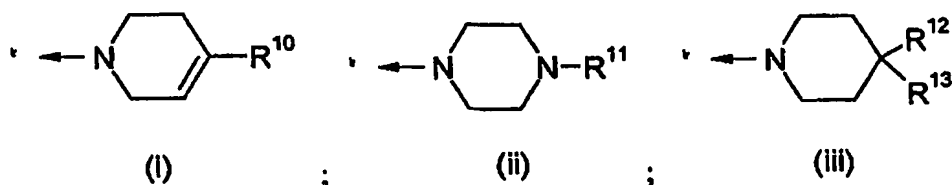
(I)

or a salt thereof, such as a pharmaceutically acceptable salt;

wherein

- $R^1$ - $R^5$  are independently selected from hydrogen, halogen, cyano, nitro,  $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, or  $C_{2-6}$ -alkynyl; such as methyl),  $C_{3-8}$ -cycloalk(en)yl (e.g.  $C_{3-8}$ -cycloalkyl),  $C_{3-8}$ -cycloalk(en)yl- $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl), amino,  $C_{1-6}$ -alk(en/yn)ylamino (e.g.  $C_{1-6}$ -alkylamino), di-( $C_{1-6}$ -alk(en/yn)yl)amino (e.g. di-( $C_{1-6}$ -alkyl)amino),  $C_{1-6}$ -alk(en/yn)ylcarbonyl (e.g.  $C_{1-6}$ -alkylcarbonyl), aminocarbonyl,  $C_{1-6}$ -alk(en/yn)ylaminocarbonyl (e.g.  $C_{1-6}$ -alkylaminocarbonyl), di-( $C_{1-6}$ -alk(en)yl)aminocarbonyl (e.g. di-( $C_{1-6}$ -alkyl)aminocarbonyl)), hydroxy,  $C_{1-6}$ -alk(en/yn)ylloxy (e.g.  $C_{1-6}$ -alkoxy; such as methoxy),  $C_{1-6}$ -alk(en/yn)ylthio (e.g.  $C_{1-6}$ -alkylthio, such as methylthio), halo- $C_{1-6}$ -alk(en/yn)yl (e.g. halo- $C_{1-6}$ -alkyl, such as trifluoromethyl), halo- $C_{1-6}$ -alk(en/yn)ylsulfonyl (e.g. trifluoromethylsulfonyl), halo- $C_{1-6}$ -alk(en/yn)ylsulfanyl (e.g. trifluoromethylsulfanyl)), and  $C_{1-6}$ -alk(en/yn)ylsulfonyl (e.g.  $C_{1-6}$ -alkylsulfonyl);
- $R^6$  is selected from hydrogen, halo- $C_{1-6}$ -alk(en/yn)yl (e.g. trifluoromethyl),  $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{1-6}$ -alkyl, such as methyl,  $C_{2-6}$ -alkenyl, or  $C_{2-6}$ -alkynyl),  $C_{3-8}$ -cycloalk(en)yl (e.g.  $C_{3-8}$ -cycloalkyl), and  $C_{3-8}$ -cycloalk(en)yl- $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl);
- $R^7$  is an aryl or a heteroaryl; or  $R^7$  is a group aryl- $CR^8R^9$ -, wherein  $R^8$  and  $R^9$  is independently selected from hydrogen,  $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, or  $C_{2-6}$ -alkynyl; such as methyl),  $C_{3-8}$ -cycloalk(en)yl (e.g.  $C_{3-8}$ -cycloalkyl), and  $C_{3-8}$ -cycloalk(en)yl- $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl);
- n is 0, 1, or 2, wherein n is 0 in a preferred embodiment;

Q is selected from (i)-(vii), the arrow indicating the attachment point:



wherein  $R^{10}$  is an optionally substituted aryl;

wherein  $R^{11}$  is selected from an optionally substituted aryl or optionally substituted benzyl, halo- $C_{1-6}$ -alk(en/yn)ylsulfonyl (e.g. trifluoromethylsulfonyl),  $C_{1-6}$ -alk(en/yn)ylsulfonyl (e.g.  $C_{1-6}$ -alkylsulfonyl), arylsulphonyl, arylacetyl,  $C_{1-6}$ -alk(en/yn)ylcarbonyl (e.g.  $C_{1-6}$ -alkylcarbonyl), aminocarbonyl,  $C_{1-6}$ -alk(en/yn)ylaminocarbonyl (e.g.  $C_{1-6}$ -alkylaminocarbonyl), and di- $(C_{1-6}$ -alk(en)yl)aminocarbonyl (e.g. di- $(C_{1-6}$ -alkyl)aminocarbonyl);

wherein  $R^{12}$  is an optionally substituted aryl;

wherein  $R^{13}$  is hydrogen, hydroxy, cyano, or amino, or one of the following groups:

- $NHC_{1-6}$ -alk(en/yn)yl (e.g. - $NHC_{1-6}$ -alkyl, - $NHC_{2-6}$ -alkenyl, or - $NHC_{2-6}$ -alkynyl; such as methyl);

- $N(C_{1-6}$ -alk(en/yn)yl)<sub>2</sub> (e.g. - $N(C_{1-6}$ -alkyl)<sub>2</sub>);

- $NR^{14}COR^{15}$ , wherein  $R^{14}$  is hydrogen or  $C_{1-6}$ -alk(en/yn)yl and  $R^{15}$  is  $C_{1-6}$ -alk(en/yn)yl or  $C_{3-8}$ -cycloalk(en)yl;

- $NR^{16}COCONR^{17}R^{18}$ , wherein  $R^{16}$  is hydrogen or  $C_{1-6}$ -alk(en/yn)yl and  $R^{17}$  and  $R^{18}$  are selected independently from hydrogen and  $C_{1-6}$ -alk(en/yn)yl (e.g.  $C_{1-6}$ -alkyl)

or C<sub>3-8</sub>-cycloalkyl; or R<sup>17</sup> and R<sup>18</sup> together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted (i.e. unsubstituted or substituted) with a C<sub>1-6</sub>-alk(en/yn)yl.

5 -NR<sup>19</sup>CONR<sup>20</sup>R<sup>21</sup>, wherein R<sup>19</sup> is hydrogen or C<sub>1-6</sub>-alk(en/yn)yl and R<sup>20</sup> and R<sup>21</sup> are selected independently from hydrogen and C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl; or R<sup>20</sup> and R<sup>21</sup> together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted (i.e. unsubstituted or substituted) with a  
10 C<sub>1-6</sub>-alk(en/yn)yl;

-NR<sup>22</sup>SO<sub>2</sub>R<sup>23</sup>, wherein R<sup>22</sup> is hydrogen or C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl and R<sup>23</sup> is amino, C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl;

-COR<sup>24</sup>, wherein R<sup>24</sup> is C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl;

-CONR<sup>25</sup>R<sup>26</sup>, wherein R<sup>25</sup> and R<sup>26</sup> independently are selected from hydrogen, C<sub>1-6</sub>-alk(en/yn)yl and C<sub>3-8</sub>-cycloalkyl, or R<sup>25</sup> and R<sup>26</sup> together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted (i.e. unsubstituted or substituted) with a C<sub>1-6</sub>-alk(en/yn)yl, in particular C<sub>1-6</sub>-alkyl;

wherein X, Y, and Z are selected independently from a bond; O; NR<sup>27</sup>; CR<sup>28</sup>R<sup>29</sup> and  
20 S(O)<sub>m</sub>,

wherein m is 0, 1 or 2;

wherein R<sup>27</sup> is selected from hydrogen, C<sub>1-6</sub>-alk(en/yn)yl (such as C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, or C<sub>2-6</sub>-alkynyl), C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl; or

25 R<sup>27</sup> is a group R<sup>30</sup>SO<sub>2</sub>-, R<sup>30</sup>OCO- or R<sup>30</sup>SCO-, wherein R<sup>30</sup> is C<sub>1-6</sub>-alk(en/yn)yl (such as C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, or C<sub>2-6</sub>-alkynyl), C<sub>3-8</sub>-cycloalkyl, or C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl; or

R<sup>27</sup> is a group R<sup>31</sup>R<sup>32</sup>NCO- or R<sup>31</sup>R<sup>32</sup>NCS-, wherein R<sup>31</sup> and R<sup>32</sup> are independently selected from hydrogen, C<sub>1-6</sub>-alk(en/yn)yl (such as C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, or C<sub>2-6</sub>-alkynyl), C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl and aryl, wherein said  
30 aryl is optionally substituted (i.e. unsubstituted or substituted), e.g. with one or more substituents selected from C<sub>1-6</sub>-alkyl or halogen; or wherein R<sup>31</sup> and R<sup>32</sup>

together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group;  
 wherein  $R^{28}$  and  $R^{29}$  are independently selected from hydrogen, halo such as fluoro,  $C_{1-6}$ -alk(en/yn)yl (such as  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkenyl, or  $C_{2-6}$ -alkynyl),  
 5  $C_{3-8}$ -cycloalkyl, and  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl;  
 wherein  $R^{33}$ - $R^{36}$  are independently selected from hydrogen, halogen, cyano, nitro,  $C_{1-6}$ -alk(en/yn)yl (such as  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, or  $C_{2-6}$ -alkynyl),  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl-alkyl, amino,  $C_{1-6}$ -alkylamino, di- $(C_{1-6}$ -alkyl)amino,  $C_{1-6}$ -alkylcarbonyl, aminocarbonyl,  $C_{1-6}$ -alkylaminocarbonyl, di- $(C_{1-6}$ -alkyl)aminocarbonyl,  $C_{1-6}$ -alkoxy,  $C_{1-6}$ -alkylthio, hydroxy, halo- $C_{1-6}$ -alk(en/yn)yl,  
 10 preferably trifluoromethyl, trifluoromethylsulfonyl and  $C_{1-6}$ -alkylsulfonyl;  
 provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S.

- 15 To further illustrate the invention, without limitation, the following embodiments of  $R^1$ - $R^5$  are within the scope of the invention, in particular for the compounds or salt thereof:  $R^1$ - $R^5$  are independently selected from hydrogen, halogen, cyano,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyloxy,  $C_{1-6}$ -alkylthio, and trifluoromethyl;  $R^1$ - $R^5$  are independently selected from a hydrogen and  $C_{1-6}$ -alkyl;  $R^1$ - $R^5$  are independently selected from hydrogen, Cl, F, cyano, methyl, methoxy, methylthio, and trifluoromethyl;  $R^1$ - $R^5$  are hydrogen;  $R^1$ - $R^5$  are independently selected from hydrogen and halogen;  $R^1$ - $R^5$  are independently selected from hydrogen, chloro and fluoro;  $R^1$ - $R^5$  are independently selected from hydrogen and chloro;  $R^1$ - $R^5$  are independently selected from hydrogen and fluoro;  $R^2$  is chloro and  $R^3$  is hydrogen,  $R^2$  and  $R^3$  are chloro,  $R^2$  is fluoro and  $R^3$  is hydrogen, or  $R^2$  and  $R^3$  is fluoro, where the rest of  $R^1$ - $R^5$  may, e.g., be hydrogen or they may also be substituted from the list above; at least one  $R^1$ - $R^5$  is F or Cl, such as a compound of the invention for which  $R^3$  is F or Cl;  $R^1$ - $R^5$  is selected independently from H and cyano;  $R^1$ - $R^5$  is selected independently from H and  $C_{1-6}$ -alk(en/yn)yl;  $R^1$ - $R^5$  is selected independently from H and  $C_{1-6}$ -alkyl, such as methyl;  $R^1$ - $R^5$  is selected independently from H and  $C_{1-6}$ -alk(en/yn)oxy, preferably  $C_{1-6}$ -alkoxy, such as methoxy;  $R^1$ - $R^5$  is selected independently from H and  $C_{1-6}$ -alkylthio, such as methylthio;  $R^1$ - $R^5$  is selected independently from H and trifluoromethyl; at least 3 of  $R^1$ - $R^5$  is hydrogen, such as 3, 4 or all of  $R^1$ - $R^5$  is hydrogen.

To further illustrate the invention, without limitation, the following embodiments of  $R^6$  are within the scope of the invention, in particular for the compounds or salt thereof:  $R^6$  is selected from hydrogen, halo- $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, and  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl;  $R^6$  is selected from hydrogen and  $C_{1-6}$ -alk(en/yn)yl;  $R^6$  is hydrogen;  $R^6$  is a  $C_{1-6}$ -alkyl;  $R^6$  is methyl.

To further illustrate the invention, without limitation, the following embodiments of  $R^7$ , for which  $R^7$  is a group aryl- $CR^8R^9$ -, are within the scope of the invention, in particular for the compounds or salt thereof:  $R^8$  and  $R^9$  are independently selected from hydrogen,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl and  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl;  $R^8$  and  $R^9$  are independently selected from hydrogen and  $C_{1-6}$ -alkyl;  $R^8$  and  $R^9$  is independently selected from hydrogen and methyl;  $R^8$  and  $R^9$  is hydrogen;  $R^8$  is hydrogen and  $R^9$  is methyl.

It is understood that the aryl of aryl- $CR^8R^9$ - is as defined herein, i.e. it may, e.g., have one or more of the following characteristics: the aryl is monocyclic or bicyclic; the aryl is unsubstituted; the aryl is substituted with one or more substituents, preferably selected from the group consisting of halogen, cyano, nitro,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl,  $C_{2-6}$ -alkynyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl, amino,  $C_{1-6}$ -alkylamino, di- $(C_{1-6}$ -alkyl)amino,  $C_{1-6}$ -alkylcarbonyl, aminocarbonyl,  $C_{1-6}$ -alkylaminocarbonyl, di- $(C_{1-6}$ -alkyl)aminocarbonyl,  $C_{1-6}$ -alkylcarbonylamino,  $C_{1-6}$ -alkylcarbonyl  $C_{1-6}$ -alkylamino,  $C_{1-6}$ -alkoxy,  $C_{1-6}$ -alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl; the aryl is an optionally substituted phenyl; the aryl is mono- or poly-substituted, including di-substituted, e.g. with a halogen, such as fluoro or chloro.

In a preferred embodiment,  $R^7$  is an aryl- $CR^8R^9$ - selected from benzyl or halogen substituted benzyl, e.g. 4-halo benzyl, such as 4-fluorobenzyl, or 2-halo-benzyl, such as 2-chloro-benzyl.

When  $R^7$  is aryl or heteroaryl, it is understood that the aryl and heteroaryl is as defined herein and may be selected among these.

In one aspect the invention relates to embodiments of the invention where Q is (i) and the aryl of  $R^{10}$  is selected from the aryls as defined herein.

In further embodiments, the invention relates to a compound or salt of the invention wherein Q is (ii), preferably R<sup>11</sup> is selected from an optionally substituted (i.e. substituted or not) aryl or optionally substituted (i.e. substituted or not) benzyl, trifluoromethylsulfonyl, C<sub>1-6</sub>-alkylsulfonyl, arylsulphonyl, arylacyl, C<sub>1-6</sub>-alkylcarbonyl, aminocarbonyl, C<sub>1-6</sub>-alkylaminocarbonyl and di-(C<sub>1-6</sub>-alkyl)aminocarbonyl), wherein said aryl is selected from the aryls as defined herein. The benzyl may be substituted with one or more substituent selected from the substituent list as defined herein.

- 10 In further embodiments, the invention relates to a compound or salt of the invention wherein Q is (iii) or (vii), in an even more preferred embodiment Q is (iii).

To further illustrate the invention, without limitation, the following embodiments of R<sup>12</sup> are within the scope of the invention, in particular for the compounds or salt thereof: R<sup>12</sup> is an aryl as defined herein; R<sup>12</sup> is phenyl; R<sup>12</sup> is a phenyl substituted with one or more substituents, preferably selected from the substituent list as defined herein; the aryl in R<sup>12</sup> is substituted with one or more substituents selected from a halogen and trifluoromethyl; the aryl in R<sup>12</sup> is substituted with at least one chloro or at least one fluoro and at least one trifluoromethyl; the aryl in R<sup>12</sup> is substituted with one Cl and one trifluoromethyl; R<sup>12</sup> is 4-chloro-3-trifluoromethyl-phenyl.

In one embodiment when Q is (iii) the group R<sup>13</sup> is hydroxy. In a preferred embodiment R<sup>12</sup> is 4-chloro-3-trifluoromethyl-phenyl and R<sup>13</sup> is hydroxy.

- 25 In further embodiments of (iii) the R<sup>13</sup> is -NR<sup>14</sup>COR<sup>15</sup>, where R<sup>14</sup> and R<sup>15</sup> are as defined herein. To further illustrate the invention, without limitation, the following embodiments of R<sup>13</sup> are within the scope of the invention, in particular for the compounds or salt thereof: R<sup>14</sup> is hydrogen or C<sub>1-6</sub>-alkyl and R<sup>15</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-8</sub>-cycloalkyl; R<sup>14</sup> is H or CH<sub>3</sub>; R<sup>15</sup> is CH<sub>3</sub>; R<sup>14</sup> is hydrogen and R<sup>15</sup> is methyl; R<sup>14</sup> and R<sup>15</sup> are methyl.

30 In further embodiments of (iii), the R<sup>13</sup> is -NR<sup>16</sup>COCONR<sup>17</sup>R<sup>18</sup>, wherein R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> is as defined herein. To further illustrate the invention, without limitation, the following embodiments of R<sup>13</sup> are also within the scope of the invention, in particular for the



compounds or salt thereof:  $R^{16}$  is hydrogen or  $C_{1-6}$ -alkyl and wherein  $R^{17}$  and  $R^{18}$  are selected independently from hydrogen,  $C_{1-6}$ -alkyl and  $C_{3-8}$ -cycloalkyl;  $R^{16}$  is hydrogen or  $C_{1-6}$ -alkyl and where  $R^{17}$  and  $R^{18}$  together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, where said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $C_{1-6}$ -alkyl, e.g. methyl;  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are hydrogen (i.e. oxalamide,  $-NHCOCONH_2$ );  $R^{16}$  is  $C_{1-6}$ -alkyl, and  $R^{17}$  and  $R^{18}$  are hydrogen (i.e.  $N$ - $C_{1-6}$ -alkyl oxalamide);  $R^{16}$  and  $R^{17}$  are hydrogen and  $R^{18}$  is  $C_{1-6}$ -alkyl (i.e.  $N'$ - $C_{1-6}$ -alkyl- $N$ -oxalamide);  $R^{16}$  and  $R^{17}$  are  $C_{1-6}$ -alkyl and  $R^{18}$  is hydrogen (i.e.  $N'$ - $C_{1-6}$ -alkyl- $N$ - $C_{1-6}$ -alkyl oxalamide);  $R^{16}$  is hydrogen and  $R^{17}$  and  $R^{18}$  are  $C_{1-6}$ -alkyl, e.g. methyl, (i.e.  $N',N'$ -di- $(C_{1-6}$ -alkyl)- $N$ -oxalamide);  $R^{16}$  is hydrogen and  $R^{17}$  and  $R^{18}$  are methyl;  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  is  $C_{1-6}$ -alkyl (i.e.  $N',N'$ -di- $(C_{1-6}$ -alkyl)- $N$ - $C_{1-6}$ -alkyl oxalamide).

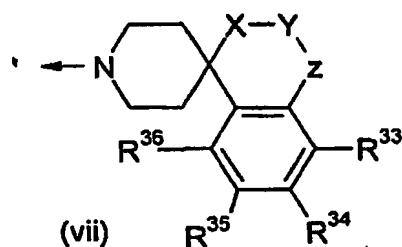
In further embodiments of (iii) the  $R^{13}$  is  $-NR^{19}CONR^{20}R^{21}$ , wherein  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  is as defined herein. To further illustrate the invention, without limitation, the following embodiments of  $R^{13}$  are also within the scope of the invention, in particular for the compounds or salt thereof:  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are independently selected from hydrogen,  $C_{1-6}$ -alkyl and  $C_{3-8}$ -cycloalkyl;  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are independently selected from hydrogen and  $C_{1-6}$ -alkyl;  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are hydrogen;  $R^{19}$  is a  $C_{1-6}$ -alkyl and  $R^{20}$  and  $R^{21}$  are hydrogen;  $R^{19}$  and  $R^{20}$  are hydrogen and  $R^{21}$  is a  $C_{1-6}$ -alkyl;  $R^{19}$  and  $R^{20}$  is independently selected from a  $C_{1-6}$ -alkyl and  $R^{21}$  is H;  $R^{19}$  is H, and  $R^{20}$  and  $R^{21}$  is independently selected from a  $C_{1-6}$ -alkyl; or  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  is independently selected from a  $C_{1-6}$ -alkyl;  $R^{19}$  is H and  $R^{20}$  and  $R^{21}$  are independently selected from the group consisting of hydrogen, Me, Et, Bu, and i-Pr.

In further embodiments of (iii) the  $R^{13}$  is  $-NR^{22}SO_2R^{23}$ , wherein  $R^{22}$  and  $R^{23}$  are as defined herein. To further illustrate the invention, without limitation, the following embodiments of  $R^{13}$  are also within the scope of the invention, in particular for the compounds or salt thereof:  $R^{22}$  is hydrogen or a  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl and  $R^{23}$  is amino,  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl;  $R^{22}$  is hydrogen and  $R^{23}$  is a  $C_{1-6}$ -alkyl, e.g. methyl (i.e.  $N$ -( $C_{1-6}$ -alkylsulphonamide) or  $R^{22}$  and  $R^{23}$  are independently selected from a  $C_{1-6}$ -alkyl, e.g. methyl i.e.  $N$ - $C_{1-6}$ -alkyl ( $C_{1-6}$ -alkylsulphonamide);  $R^{22}$  is hydrogen;  $R^{23}$  is methyl;  $R^{22}$  and  $R^{23}$  is methyl;  $R^{22}$  is hydrogen and  $R^{23}$  is methyl.

In further embodiments of (iii) the  $R^{13}$  is  $-\text{COR}^{24}$ , wherein  $R^{24}$  is as defined herein. The following embodiments of  $R^{13}$  are also within the scope of the invention without limitation, in particular for the compounds or salt thereof:  $R^{24}$  is a  $\text{C}_{1-6}$ -alkyl;  $R^{24}$  is methyl.

- 5 In further embodiments of (iii) the  $R^{13}$  is  $-\text{CONR}^{25}\text{R}^{26}$ , wherein  $R^{25}$  and  $R^{26}$  are as defined herein. To further illustrate the invention, without limitation, the following embodiments of  $R^{13}$  are also within the scope of the invention, in particular for the compounds or salt thereof:  $R^{25}$  and  $R^{26}$  are independently selected from hydrogen,  $\text{C}_{1-6}$ -alkyl and  $\text{C}_{3-8}$ -cycloalkyl;  $R^{25}$  and  $R^{26}$  are independently selected from hydrogen and methyl;  $R^{25}$  and  $R^{26}$  is hydrogen;  $R^{25}$  and  $R^{26}$  is methyl;  $R^{25}$  is methyl and  $R^{26}$  is hydrogen;  $R^{25}$  and  $R^{26}$  together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $\text{C}_{1-6}$ -alkyl, in a preferred embodiment the piperidinyl, piperazinyl and morpholinyl is not substituted;  $R^{25}$  and  $R^{26}$  together with the nitrogen to which they are attached form a
- 10 is hydrogen;  $R^{25}$  and  $R^{26}$  is methyl;  $R^{25}$  is methyl and  $R^{26}$  is hydrogen;  $R^{25}$  and  $R^{26}$  together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $\text{C}_{1-6}$ -alkyl, in a preferred embodiment the piperidinyl, piperazinyl and morpholinyl is not substituted;  $R^{25}$  and  $R^{26}$  together with the nitrogen to which they are attached form a
- 15 piperidinyl, wherein the piperidinyl is optionally substituted with a  $\text{C}_{1-6}$ -alkyl, however preferably the piperidinyl is unsubstituted.

In further embodiments, the invention relates to a compound or salt of the invention wherein Q is (vii) as described above.



To further illustrate the invention, without limitation, the following embodiments of (vii) are within the scope of the invention: Y is a bond and X and Z are selected independently from O,  $\text{NR}^{27}$ , and  $\text{CR}^{28}\text{R}^{29}$  and  $\text{S}(\text{O})_m$ , provided that X and Z may not at the same time be selected from O and S; Y is a bond and X and Z are selected independently from  $\text{CR}^{28}\text{R}^{29}$  and  $\text{NR}^{27}$ ; X is  $\text{CR}^{28}\text{R}^{29}$ , Y is a bond and Z is  $\text{NR}^{27}$ ; X is  $\text{CR}^{28}\text{R}^{29}$ , Y is a bond and Z is O; X is O, Y is a bond and Z is  $\text{CR}^{28}\text{R}^{29}$ ;  $\text{R}^{28}$  and  $\text{R}^{29}$  are hydrogen;  $\text{R}^{27}$  is an acyl, e.g.  $\text{C}_{1-6}$ -alkylcarbonyl; Z is  $\text{NR}^{27}$  where  $\text{R}^{27}$  is a  $\text{C}_{1-6}$ -alkylcarbonyl, e.g.  $-\text{COCH}_3$ ; X is  $\text{CR}^{28}\text{R}^{29}$  where  $\text{R}^{28}$  and  $\text{R}^{29}$  are hydrogen, Y is a bond, and Z is  $-\text{NR}^{27}$  where said  $\text{R}^{27}$  is  $-\text{COCH}_3$ ;  $\text{R}^{27}$

20

25

is selected from the group  $R^{30}SO_2-$ ,  $R^{30}OCO-$  and  $R^{30}SCO-$ ;  $R^{27}$  is  $R^{30}SO_2$ ;  $R^{30}$  is  $C_{1-6}$ -alkyl, e.g. methyl; X is  $CR^{28}R^{29}$ , Y is a bond and Z is  $NR^{27}$ , preferably  $R^{28}$  and  $R^{29}$  are hydrogen;  $R^{27}$  is the group  $R^{31}R^{32}NCO-$  or  $R^{30}R^{31}NCS-$ ; Y is a bond;  $R^{33}-R^{36}$  are independently selected from hydrogen and halogen, e.g. chloro or fluoro.

5

In further embodiments of formula I, the compound is any one of:

1. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
2. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 10 3. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
4. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 15 5. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
6. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
7. 1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 20 8. 2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
9. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 25 10. 2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
11. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
12. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 30 13. 1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

14. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
15. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 5 16. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
17. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
18. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;
- 10 19. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
20. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
- 15 21. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
22. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
23. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 20 24. 2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
25. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 25 26. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
27. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
28. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 30 29. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

30. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
31. 1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 5 32. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
33. 1-(3,4-Difluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid -methyl-amide;
34. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 10 35. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
36. 1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 15 37. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
38. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
- 20 39. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;
40. 1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
41. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
- 25 42. 1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
43. 1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 30 44. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
45. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

46. 1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
47. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 5 48. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;
49. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
50. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 10 51. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
52. 1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 15 53. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
54. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;
55. 1-(3,4-Dichloro-phenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and
- 20 56. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide; or a salt thereof, such as a pharmaceutically acceptable salt.
- 25 In an even more preferred embodiment of formula I, the compound is any one of the following compounds:
- 1a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 2a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 30 3a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

- 4a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 5a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
- 5 6a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
- 7a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 10 8a. (1S,2R)-2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 9a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 10a. (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 15 11a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 12a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 20 13a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 14a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 15a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 25 16a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 17a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 30 18a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;
- 19a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

- 20a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
- 21a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-  
5 cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 22a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 23a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 10 24a. (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 25a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 26a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-  
15 phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 27a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 28a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-  
20 cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 29a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 30a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-  
25 amide;
- 31a. (1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 32a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-  
30 amide;
- 33a. (1S,2R)-1-(3,4-Difluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid -methyl-amide;



- 34a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 5 35a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 36a. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 10 37a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 38a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
- 15 39a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;
- 40a. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-C23-amide+C31;
- 41a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
- 20 42a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 43a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 44a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
- 25 45a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 46a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 30 47a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

- 48a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;
- 49a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 50a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 51a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 52a. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 53a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
- 54a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;
- 55a. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 56a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide.
- 57a. (1S,2R)- 2-(4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-ethyl-amide
- 58a. (1S,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide -([R]-1-phenyl-ethyl) amide
- 59a. (1R,2S)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- 60a. (1R,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and
- 61a. (1S,2S)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
- or a salt thereof, such as a pharmaceutically acceptable salt.

The present invention also comprises salts of the compounds of the invention, typically, pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid

addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

- 5 Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like.

Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic,  
10 maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pantoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of  
15 pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

20

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

- 25 Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In  
30 general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

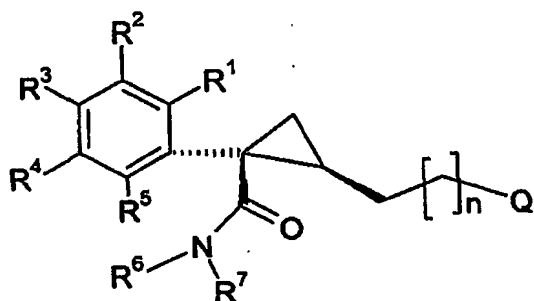
The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures, i.e. a mixture of stereoisomers, are included within the scope of the invention

5

The compounds of the general formula I exist as optical isomers thereof and such optical isomers are also embraced by the invention. In particular, the compounds of the invention possessing the absolute stereochemistry (1S,2R) are within the invention, either as enantiomers or as mixtures containing compounds of the invention possessing the absolute stereochemistry (1S,2R).

10

Accordingly an important aspect of the invention is a compound or salt of the invention as described herein, wherein the compound of formula I is the (1S,2R)-isomer i.e. the compound with absolute configuration as shown in formula IA.



(IA)

15

The compound of the invention of formula I or the salt thereof may be part of a racemic mixtures comprising the (1S,2R)-isomer, i.e. the compound shown in formula IA or it may be present as the enantiomer, i.e. without the 3 others stereoisomers.

20

The expression "mixture of stereoisomers comprising the (1S,2R)-isomer of formula 1" implies that in further embodiments, the compound of the invention, i.e. product, may be any one of the following mixture of stereoisomers: a (1S,2R)-isomer and a (1R,2R)-isomer of formula 1; a (1S,2R)-isomer and a (1R,2S)-isomer of formula 1; a (1S,2R)-isomer and a (1S,2R)-isomer of formula 1; a (1S,2R)-isomer and a (1S,2S)-isomer of formula 1; a (1S,2R)-isomer and a (1R,2R)-isomer of formula 1, i.e. consisting of 2, 3 or 4 of the corresponding stereoisomers.

25

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active  
5 matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives. Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates,  
10 and Resolutions", John Wiley and Sons, New York (1981). Optically active compounds can also be prepared from optically active starting materials.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers,  
15 as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

20 Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on  
25 administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example,  
30 in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The compounds (including salts thereof) of the invention are NK3 receptor antagonists having a human NK3 binding affinity (IC<sub>50</sub>) of 5  $\mu$ M or less, typically of 1  $\mu$ M or less, and preferably of 200 nM or less, e.g. as measured by the method described in Example 15.

- 5 A further objective of the present invention is to provide compounds, including salts thereof, with such activities which have one or more of the following parameters which are improved: solubility, metabolic stability and bioavailability compared to prior art compounds.

10 **Pharmaceutical use**

- As mentioned above the compounds of the invention are NK3 receptor antagonists and may thus be useful for treatment in a disorder or disease wherein the NK3 receptor is implicated. Accordingly, compounds of the invention and the salt thereof may be applicable for treatment, including prevention, of schizophrenia, psychosis, depression, anxiety,  
15 Parkinson's disease, pain, convulsions cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema or plasma extravasation. In a preferred embodiment, the compounds of the invention and the salt thereof can be used as an antipsychotic.

20

- In further embodiments, the compound of the invention or salt thereof may also have some NK1 and/or NK2 activity in addition to the NK3 activity as described herein. Accordingly, the compound of the invention and the salts thereof may also be useful for the treatment, including prevention, of diseases where the NK1 receptor and/or the NK2 receptor is  
25 implicated, especially emesis, depression or anxiety

In a further aspect, the invention relates to a compound of the invention or salts thereof for use as a medicament.

- 30 The present invention also relates to a pharmaceutical composition comprising a compound of the invention or a salt thereof and a pharmaceutically acceptable carrier or a diluent. The composition may comprise any one of the embodiments of formula I described herein.

The present invention also relates to use of a compound of the invention or a salt thereof, for the preparation of a medicament for the treatment of a disease or disorder, wherein an NK receptor antagonist, in particular an NK3 receptor antagonist is beneficial. The medicament may comprise any one of the embodiments of formula I described herein.

5

In particular the present invention relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment of: schizophrenia, psychosis, depression, anxiety, Parkinson's disease, pain, convulsions cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema or plasma extravasation. Accordingly, the present invention relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment of psychiatric diseases, hypertension and in general any central or peripheral condition in which the NK3 receptor are involved.

15

In particular, the present invention relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment of schizophrenia or psychosis. A preferred embodiment of the invention relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment of schizophrenia.

20

Further, the invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of depression or anxiety. The invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of Parkinson's disease. Further, the invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of convulsions.

25

A further aspect of the invention relates to a method for the treatment or prevention of schizophrenia, psychosis, depression, anxiety, Parkinson's disease, pain, convulsions cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema or plasma extravasation, in a living animal body, including a human, comprising administering to a subject in need thereof a therapeutically

30

effective amount of a compound of the invention or a pharmaceutically acceptable acid addition salt thereof. In general the invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of these diseases/disorders.

5

The compounds of the invention or the salt thereof may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known  
10 adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any  
15 suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and  
20 the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to  
25 provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

30

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot



injetable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels,  
5 inhalants, dermal patches, implants, etc.

In an embodiment of the pharmaceutical composition, the compound of the invention administered in an amount of from about 0.001 to about 100 mg/kg body weight per day.

10 Conveniently, the compounds of the invention are administered in a unit dosage form containing said compounds in an amount of about 0.01 to 100 mg. The total daily dose is usually in the range of about 0.05 - 500 mg.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight  
15 per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and  
20 other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably  
25 from about 0.05 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

30

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the invention contains a

free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the invention with a chemical equivalent of a pharmaceutically acceptable acid. Representative examples are mentioned above.

- 5 For parenteral administration, solutions of the compound of the invention in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal  
10 administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

- Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba,  
15 sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The  
20 pharmaceutical compositions formed by combining the compound of the invention and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

- 25 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

30

If a solid carrier is used for oral administration, the preparation may be tablette, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg

to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid  
5 suspension or solution.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

10 For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc.  
15 may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials.  
20 Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

1)	Tablets containing 5.0 mg of a compound of the invention calculated as the free 25 base:	
	Compound	5.0 mg
	Lactose	60 mg
	Maize starch	30 mg
	Hydroxypropylcellulose	2.4 mg
30	Microcrystalline cellulose	19.2 mg
	Croscarmellose Sodium Type A	2.4 mg
	Magnesium stearate	0.84 mg

- 2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

Compound	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

- 3) Syrup containing per millilitre:

Compound	25 mg
Sor bitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 mL
Flavour	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

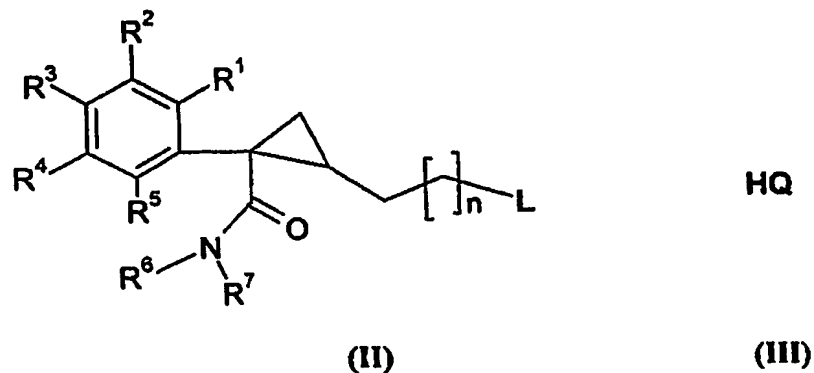
- 4) Solution for injection containing per millilitre:

Compound	0.5 mg
Sorbitol	5.1 mg
Acetic Acid	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

#### Methods of preparation of the compounds of the invention

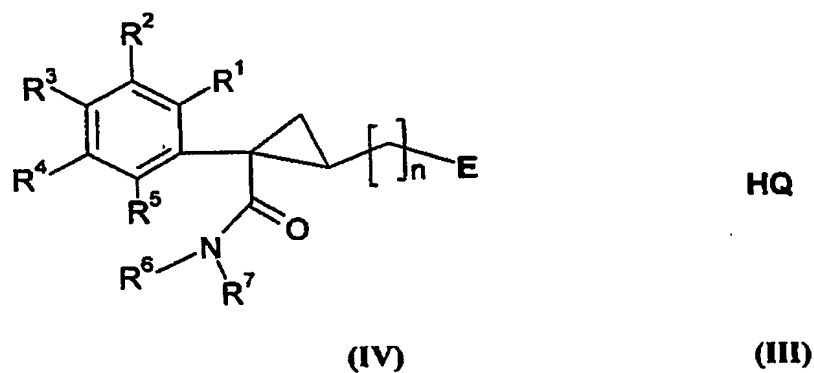
The compounds of the invention may be prepared as follows:

**Method 1** Alkylating an amine of formula III with an alkylating derivative of formula II:



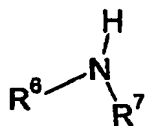
where  $R^1$ - $R^3$ ,  $n$  and  $Q$  are as defined herein, and  $L$  is a leaving group such as e.g. halogen,  
 5 mesylate or tosylate;

**Method 2** Reductive alkylation of an amine of formula III with a reagent of formula IV:

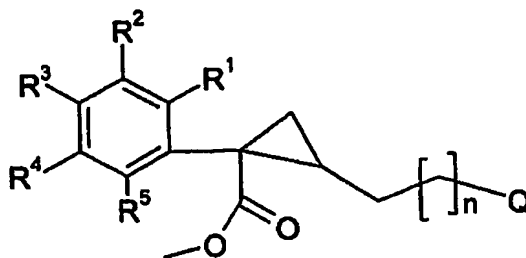


10 where  $R^1$ - $R^3$ ,  $n$  and  $Q$  are as defined herein, and  $E$  is an aldehyde or an activated carboxylic acid;

**Method 3** Reacting an amine of formula VI with an methyl ester of formula VII by the use of Lewis acid catalyst:



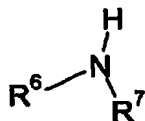
(VI)



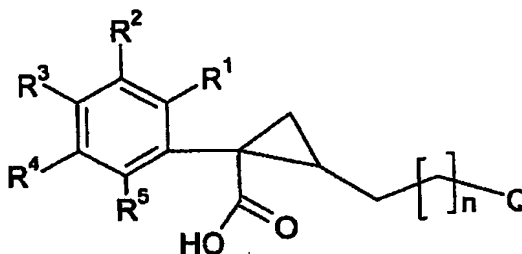
(VII)

where  $R^1$ - $R^{36}$ ,  $n$  and  $Q$  are as defined herein,

**Method 4** Reacting an amine of formula VI with an acid of formula VIII by the use of an activating reagent or a coupling reagent:



(VI)



(VIII)

wherein  $R^1$ - $R^{36}$ ,  $n$  and  $Q$  are as defined herein,

whereupon the compound of formula I is isolated as the free base or a pharmaceutically acceptable acid addition salt thereof.

The alkylation according to **method 1** is conveniently performed in an organic solvent such as a suitably boiling alcohol or ketone, preferably in the presence of an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature, which is different from the boiling point, in one of the above-mentioned solvents or in dimethyl formamide (DMF), dimethylsulfoxide (DMSO), or N-methylpyrrolidin-2-one (NMP), preferably in the presence of a base. The alkylating derivatives of formula II with  $n=0$  have been described in the literature or can be prepared in an analogous manner e.g. Shuto *et al. J. Org. Chem.*

- 1996, 61, 915 and Ronsisvalle *et al. Biorg. Med. Chem.* 2000, 8, 1503 and Bonnaud *et al. J. Med. Chem.* 1987, 30, 318. The alkylating derivatives of formula II with  $n=1$  and  $n=2$  can be prepared from alkylating derivatives of formula II with  $n=0$  by standard chain elongation methods e.g. by substitution of an bromide of formula II with  $n=0$  with cyanide followed by
- 5 hydrolysis, reduction to the alcohol and conversion to a leaving group L resulting in alkylating derivatives of formula II with  $n=1$ . Correspondingly, alkylating derivatives of formula II with  $n=2$  can be prepared by substitution of an bromide of formula II with  $n=0$  with a malonic ester derivative, followed by hydrolysis, decarboxylation, reduction to the alcohol and conversion to a leaving group L. Standard chain elongation methods are
- 10 described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; or Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions.
- 15 The amines of formula III are either commercially available or can be prepared by methods analogues to those described in the literature e.g. Marxer *et al. J. Org. Chem.* 1975, 40, 1427, by Parham *et al. J. Org. Chem.* 1976, 41, 2628 and by Bauer *et al. J. Med. Chem.* 1976, 19, 1315, Maligres *et al. Tetrahedron* 1997, 53, 10983, and by Cheng *et al. Tet. Lett.* 1997, 38, 1497, Chen, Meng-Hsin; Abraham, John A. *Tetrahedron Lett.* 1996, 37, 5233-
- 20 5234 and Slade, P.D. *et al. J. Med. Chem.* 1998, 41, 1218-1235 or as described by the methods used in the examples or analogues methods.

The reductive alkylation according to **method 2** is performed by standard literature methods. Aldehydes or acids of the formula IV can be prepared by methods analogues to

25 those described in e.g. Shuto *et al. J. Org. Chem.* 1996, 61, 915 and Shuto *et al. J. Med. Chem.* 1996, 38, 2964 and Shuto *et al. J. Chem. Soc., Perkin Trans. 1*, 2002, 1199 and Bonnaud *et al. J. Med. Chem.* 1987, 30, 318. The reaction can be performed in two steps, e.g. coupling of amines of formula III with reagent of formula IV by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in

30 combination with a coupling reagents such as e.g. dicyclohexyl carbodiimide, followed by reduction of the resulting amide with lithium aluminium hydride or alane. Alternatively, the reaction can be performed in one step by reductive amination of an aldehyde of formula IV with an amine of formula III according to methods described in standard works such as

Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions.

- 5 The acylation of amine VI in **method 3** with an ester of formula VII can be performed by methods analogous to those described in the literature e.g. Lesimple *et al. Synthesis* 1991, 306. Amines of formula VI are either commercially available or can be prepared by methods known in the literature according to methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely  
10 under reaction conditions such as those which are known and suitable for such reactions and esters of formula VII can be made by methods analogous to those described in the literature e.g. Shuto *et al. J. Org. Chem.* 1996, 61, 915 and Ronsisvalle *et al. Biorg. Med. Chem.* 2000, 8, 1503 and Bonnaud *et al. J. Med. Chem.* 1987, 30, 318.

15

- The acylation of amine VI in **method 4** with an acid of formula VIII can be performed by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with a coupling reagents such as e.g. dicyclohexyl carbodiimide, carbonyl diimidazole or benzotriazol-1-oxyltris(dimethylamino)phosphonium  
20 hexafluorophosphate as described in standard works e.g. Bodanszky "*The practice of peptide synthesis*", 1994 Springer verlag Berlin, ISBN 3-540-57505-7 and Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York. The acid of formula VIII can be prepared by standard basic hydrolysis of the ester described in **method**  
25 **3** and in the Examples.

The invention disclosed herein is further illustrated by the following non-limiting examples.

## EXAMPLES

### 30 General Methods

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (C18



column 4.6 × 30 mm with a particle size of 3.5 μm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 4 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times,  $R_t$ , are expressed in minutes.

5

Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion,  $MH^+$ , was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100-200V).

10 Preparative LC-MS-separation was performed on the same instrument. The LC conditions (C18 column 20 × 50 mm with a particle size of 5 μm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (5:95:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

15

$^1H$  NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations  
20 are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat.  
25 No. 220776) was used. Prior use of the SCX-columns was pre-conditioned with 10% solution of acetic acid in methanol (3 mL).

### Preparation of intermediates

#### Example 1    Synthesis of racemic 1-(3,4-Difluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one

30

(3,4-Difluorophenyl)acetic acid (52 g; 0.3 mol) was dissolved in *N,N*-dimethylformamid (200 mL). Potassium carbonate (61 g, 0.45 mol) was added and the mixture was stirred at room temperature (rt) for 15 min. Allyl bromide (47 g, 0.39 mol) was added and the

suspension was stirred at room temperature for 20 h. The mixture was thrown into water (250 mL) and extracted with diethylether (2X 300 mL). The combined organic phases were washed with water (4 x 100 mL), dried (Magnesium sulphate) and evaporated *in vacuo* to give 64 g (3,4-Difluoro-phenyl)acetic acid allyl ester as a clear oil.

5

(3,4-Difluoro-phenyl)acetic acid allyl ester (64g) was dissolved in acetonitrile (400 mL) and 4-acetamidobenzenesulfonyl azide (p-ABSA, 87 g, 0.36 mol) was added and the mixture stirred at room temperature for 15 min. The mixture was then cooled to 0°C and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 58.6 mL) was added dropwise at 0°C during 30 min.

10 The mixture was allowed to warm up to rt (room temperature) and stirred at rt for 4-20 h (until TLC showed completion of reaction). Saturated ammonium chloride (500 mL) was added and the organic phase was separated from the water phase. The water phase was extracted with diethylether (3 x 200 mL) and the four combined organic phases was dried (Magnesium sulphate) and evaporated *in vacuo*. The resulting solid was extracted with a  
15 50:50 mixture of diethylether/pentane (3 x 200 mL). The combined ether phases were evaporated *in vacuo* (keep temperature below 40°) and purified by flash column chromatography (silicagel, eluent: 10:90 mixture of diethylether/pentane). The yellow fractions were combined and evaporated *in vacuo* (keep temperature below 40°) to give 70 g diazo-(3,4-Difluoro-phenyl)acetic acid allyl ester.

20

Diazo-(3,4-Difluoro-phenyl)acetic acid allyl ester (70 g) was dissolved in dichloromethane (1000 mL) and added slowly during 36 h via a syringe pump (alternatively it is added dropwise via an addition funnel; 30 mL pr. hour) to a refluxing solution of rhodium (II) octanoate dimer (1.17 g, 1.5 mmol) in dichloromethane (200 mL). After all diazo compound  
25 has been added, the mixture is refluxed for another 30 min, then was evaporated *in vacuo* and crystallised by addition of cyclohexane (200 mL). This gave 30 g crystalline. Further 15 g was isolated from the motherliq. by repeated evaporation and crystallisation giving in total 45 g 1-(3,4-Difluoro-phenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one.

The following compounds were prepared in a similar way:

- 30 1-(3,4-dichlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
1-(4-chlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
1-(4-fluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
1-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one

**Example 2    Synthesis of (1*S*,5*R*)-1-(3,4-Dichlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one**

A solution of 3,4-dichlorophenylacetonitrile (62 g, 332 mmol) in benzene (250 mL) was added slowly to a suspension of sodium amide (28.1 g, 720 mmol) in benzene (250 mL) at 0 °C under argon, and the mixture was stirred at room temperature for 3 h. To the resulting mixture, a solution of (R)-epichlorohydrin (30.1 g, 288 mmol) in benzene (250 mL) was added at 0 °C during 45 minutes, and the whole was stirred at room temperature for 16 h. After the solvent was evaporated, EtOH (1250 mL) and 2 N NaOH (500 mL) were added to the residue, and the mixture was heated under reflux for 15 h and then acidified with 12 N HCl at 0°C (pH of the mixture was about 1). The resulting mixture was evaporated, and AcOEt (900 mL) was added to the residue. Insoluble salts were filtered off, and the filtrate was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/heptane, 20:80) to give the product as orange crystals (31.2 g, 39%). mp °C.  $[\alpha]_{20D} = -69.5$  (*c* 1.0, MeOH). 1 H-NMR (500 MHz, DMSO-*d*<sub>6</sub>) 1.38 (1 H, dd), 1.75 (1 H, dd), 2.85 (1 H, ddd), 4.25 (1 H, d), 4.46 (1 H, dd), 7.45 (1 H, d), 7.65 (1 H, d), 7.75 (1 H, s),

The following compounds were prepared in a similar way:

- (1*S*,5*R*)-1-(4-chlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
(28 g, 41%). mp °C.  $[\alpha]_{20D} = -66.1$  (*c* 1.0, MeOH). 1 H-NMR (500 MHz, CDCl<sub>3</sub>) 1.35 (1 H, dd), 1.60 (1 H, dd), 2.55 (1 H, ddd), 4.25 (1 H, d), 4.40 (1 H, dd), 7.30-7.44 (5 H, m)
- (1*S*,5*R*)-1-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one  
(36 g, 41%). mp 56-57 °C.  $[\alpha]_{20D} = -77.3$  (*c* 1.0, MeOH). 1 H-NMR (500 MHz, CDCl<sub>3</sub>) 1.45 (1 H, dd), 1.65 (1 H, dd), 2.55 (1 H, ddd), 4.30 (1 H, d), 4.45 (1 H, dd), 7.30-7.44 (5 H, m)
- (1*S*,5*R*)-1-(4-fluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
 $[\alpha]_{20D} = -63.9$  (*c* 1.0, MeOH).
- (1*S*,5*R*)-1-(3,4-difluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
 $[\alpha]_{20D} = -55.7$  (*c* 1.0, MeOH).
- (1*S*,5*R*)-1-(4-methylphenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one  
(1*S*,5*R*)-1-(4-methoxyphenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one

**Example 3 (1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid  
benzyl-methyl-amide**

To a solution of (1S,5R)-1-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (10.5 g, 60.0 mmol) in  
5 CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added AlCl<sub>3</sub> (16.0 g, 120 mmol) and then the mixture was cooled to  
0° C, and then benzyl methyl amine (240 mmol, as a 2.0M solution of benzyl methyl amine  
in THF) was added slowly. The mixture was stirred at room temperature for 24 h, and then  
the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl. After addition of CH<sub>2</sub>Cl<sub>2</sub> and  
H<sub>2</sub>O, the resulting mixture was partitioned. The organic layer was washed with 1N HCl and  
10 brine, dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel;  
AcOEt/hexane, 1:4) to give (1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic  
acid benzyl-methyl-amide.

The following compounds were prepared in a similar way:

- 15 (1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl methyl  
amide;  
(1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl methyl  
amide;  
20 (1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl  
methyl amide;  
(1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl  
methyl amide;  
(1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid methyl (1-phenylethyl)  
25 amide;  
(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-  
phenylethyl) amide;  
(1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-  
phenylethyl) amide;  
30 (1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-  
phenylethyl) amide;  
(1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-  
phenylethyl) amide;

(1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

5 (1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

10 (1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

15 (1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

(1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

20 (1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide.

#### Example 4 Esters of the formula VII

(1S,5R)-1-(3,4-Dichlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one (22.6 g) was dissolved in  
25 33% HBr/glacial acetic acid and heated to 80°C for 5h, cooled to rt and thrown into 1300 ml  
ice-water and stirred at rt for 16 h. The precipitated acid was isolated by filtration,  
redissolved in toluene (1000 ml), dried over anhydrous magnesium sulphate and evaporated  
*in vacuo* to give 30 g of the intermediate (1S,2R)-2-(bromomethyl)-1-(3,4-  
dichlorophenyl)cyclopropanecarboxylic acid. The (1S,2R)-2-(bromomethyl)-1-(3,4-  
30 dichlorophenyl)cyclopropanecarboxylic acid (30 g) was dissolved in anhydrous toluene  
(200 ml) and thionylchloride (18 ml) was added dropwise during 15 min. after which the  
mixture was refluxed for 60 min. The reaction mixture was cooled to 5°C and methanol  
(200 ml) was added and the mixture was allowed to warm to rt and stirred at rt for 2 h. The  
mixture was evaporated *in vacuo*, redissolved in diethylether, washed with saturated

aqueous sodium hydrogen carbonate 25 ml), brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. To give the intermediate (1S,2R)-2-(bromomethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid methyl ester (27 g). The (1S,2R)-2-(bromomethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid methyl ester (15 mmol) was dissolved in acetonitrile (50 ml) and added to a mixture an amine of formula III (15 mmol) in a mixture of acetonitrile (50 ml) and ethyl diisopropylamine (30 mmol). The mixture was stirred at room temperature for 16 h, evaporated *in vacuo*, taken up in ethyl acetate (200 ml) and washed successively with saturated sodium hydrogen carbonate (50 ml) and brine (50 ml, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to give the crude product ester of formula VII. Esters of formula VII were generally purified by precipitation of the oxalate salt from acetone. Other esters of formula VII could be prepared by this method by using the appropriately substituted (1S,5R)-1-aryl-3-oxa-bicyclo[3.1.0]hexan-2-one and amine of formula III.

#### 15 Example 5 Acids of the formula VIII

The oxalate salt of (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid methyl ester (10 mmol) was dissolved in methanol (80 mL) and water (20 ml). Lithium hydroxide (50 mmol) was added and the mixture was heated to reflux for 2 h. The mixture was cooled to rt and acidified to pH 3 with concentrated hydrochloric acid and the precipitated product (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid hydrochloride was isolated by filtration and dried *in vacuo*.

Other acids of formula VIII could be prepared by this method by using the appropriately substituted esters of formula VII.

#### Example 6 Piperidines of the formula III

The spiro piperidine-derivatives HQ of formula (vii), wherein X is oxygen, Z is  $CR^{27}R^{28}$ , Y is a bond, i.e. spiro[isobenzofuran-1(3H),4'-piperidines] are prepared according to the methods described by Marxer et al. *J. Org. Chem.* 1975, 40, 1427, by Parham et al. *J. Org. Chem.* 1976, 41, 2628 and by Bauer et al. *J. Med. Chem.* 1976, 19, 1315.

The following compounds were prepared in a similar way:

6-Fluorospiro[isobenzofuran-1(3H),4'-piperidine],

- 6-trifluoromethylspiro[isobenzofuran-1(3H),4'-piperidine],  
 6-fluoro-3-methylspiro[isobenzofuran-1(3H),4'-piperidine],  
 6-trifluoromethyl-3-methylspiro[isobenzofuran-1(3H),4'-piperidine],  
 5-methylspiro[isobenzofuran-1(3H),4'-piperidine],  
 5 6-fluoro-3-isobutylspiro[isobenzofuran-1(3H),4'-piperidine],  
 6-fluoro-3-cyclohexylspiro[isobenzofuran-1(3H),4'-piperidine] and  
 6-fluoro-3-(4-fluorophenyl)spiro[isobenzofuran-1(3H),4'-piperidine]

The spiro piperidine-derivatives HQ of formula (vii), wherein X is  $CR^{27}R^{28}$ , Z is  $NR^{26}$ , Y is  
 10 a bond are prepared according to the methods described by Maligres et al. *Tetrahedron*  
 1997, 53, 10983, and by Cheng et al. *Tet. Lett.* 1997, 38, 1497.

The following compounds were prepared in a similar way:

- 1-Acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,4'-piperidine];  
 15 1-Acetyl-spiro[2,3-dihydro-1H-indol-3,4'-piperidine];  
 1-Methanesulphonyl-spiro[2,3-dihydro-1H-indol-3,4'-piperidine].

The spiro piperidine-derivatives HQ of formula (vii), wherein the X is  $CR^{27}R^{28}$ , Z is oxygen,  
 Y is a bond, i.e. 2,3-dihydro-spiro(benzofuran-3,4'-piperidines), are prepared according to  
 20 the methods described by Chen, Meng-Hsin; Abraham, John A. *Tetrahedron Lett.* 1996, 37,  
 5233-5234 and Slade, P.D. et al. *J. Med. Chem.* 1998, 41, 1218-1235.

The following compounds were prepared in a similar way:

- 2,3-Dihydro-5-fluorospiro[benzofuran-3,4'-piperidine] and  
 25 2,3-dihydro-5,6-difluorospiro[benzofuran-3,4'-piperidine]

The substituents  $R^{33}-R^{36}$  are introduced by applying suitably substituted starting compounds  
 to methods analogous to the above mentioned.

### 30 Example 7 1-(tert-butoxycarbonyl)-4-isocyanato-4-phenyl-piperidine

Triethylamine (5.02mL, 36.1mmol) and diphenylphosphoryl azide (4.24mL, 19.7mmol) is  
 added to a solution of 1-(tert-butoxycarbonyl)-4-phenyl-4-piperidinecarboxylic acid (5.0g,  
 16.4mmol) in dry DMF (50mL) under nitrogen at ambient temperature. The mixture is

stirred at ambient temperature for 2h, and then heated to 60°C for 3h. The mixture is slightly cooled and concentrated *in vacuo*. Water (75mL) is added to the remanence followed by extraction with ethyl acetate (2x75mL). Combined organic fractions are washed with brine (3x50mL), dried (MgSO<sub>4</sub>) and evaporated to dryness. The crude mixture is purified by silica gel chromatography eluting with ethyl acetate-heptane (1:4). This furnishes 4.8g (98%) of the wanted 1-(tert-butoxycarbonyl)-4-isocyanato-4-phenyl-piperidine as a clear oil. LC/MS (*m/z*) 203.2 (M-boc+H<sup>+</sup>); *t<sub>R</sub>* = 3.64 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.49 (s, 9H); 1.92 (bd, 2H); 2.02 (dt, 2H); 3.15 (bt, 2H); 4.17 (bs, 2H); 7.26 (dd, 1H); 7.39 (dt, 2H); 7.44 (dd, 2H).

**Example 8 Piperidines of formula III where Q is (iii), and R<sup>12</sup> is phenyl and R<sup>13</sup> is a group -NHCONR<sup>20</sup>R<sup>21</sup>**

1-(tert-butoxycarbonyl)-4-isocyanato-4-phenyl-piperidine (1 mmol) was dissolved in anhydrous THF and an amine HNR<sup>20</sup>R<sup>21</sup> (1 mmol) was added, the mixture was stirred at rt for 16 h, evaporated *in vacuo* and redissolved in a 50:50 mixture of dichloromethane and trifluoroacetic acid (10 ml) and stirred at rt for 60 min. The mixture was evaporated *in vacuo* to give the product piperidine as the trifluoroacetic acid salt.

**Example 9 (4-Phenyl-piperidine-4-yl)-piperidin-1-yl-methanone**

Under a stream of nitrogen N,N'-carbonyldiimidazole (3.62g, 22.3mmol) followed by piperidine (3.74g, 43.9mmol) is added to a solution of 1-(tert-butoxycarbonyl)-4-phenyl-4-piperidinecarboxylic acid (3.40g, 11.1mmol) in dry THF (50mL). The mixture is heated to reflux 18h, then cooled to ambient temperature and concentrated by means of evaporation. The remanence is redissolved in ethyl acetate (150mL) and successively washed with NaHCO<sub>3</sub> (50mL, aq, sat.), dilute HCl (50mL) at pH 3, brine (50mL), then dried (MgSO<sub>4</sub>)

and evaporated to dryness. This intermediate is purified by silica gel chromatography eluting with ethyl acetate-heptane-triethylamine (40:50:10) to furnish 1.01g (24%) of 4-phenyl-4-(piperidine-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester as a white crystalline solid. This is dissolved in a mixture of MeOH (10mL) and THF (10mL), then 2M HCl in MeOH (5mL) is added and the mixture is stirred at ambient temperature for 2h.

Water (20mL) is added and pH is adjusted to pH 12 by addition of 2M NaOH. The organic phase is separated and the aqueous phase is extracted with ethyl acetate (30mL). Combined organic fractions are dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to furnish 0.47g (63%) of (4-



Phenyl-piperidine-4-yl)-piperidin-1-yl-methanone. LC/MS (m/z) 273.1 (M+H<sup>+</sup>); t<sub>R</sub> = 1.65 min.

**Example 10** Piperidines of formula III where Q is (iii), and R<sup>12</sup> is phenyl and R<sup>13</sup> is a group -CONR<sup>25</sup>R<sup>26</sup>

These piperidines were prepared by the method used in Example 9 using the appropriate amine HNR<sup>25</sup>R<sup>26</sup>.

**Example 11** Piperidines of formula III where Q is (iii), and R<sup>12</sup> is phenyl and R<sup>13</sup> is a group -NR<sup>14</sup>COR<sup>15</sup>

1-Benzyl-4-phenyl-piperidin-4-ylamine (*Bioorg.Med.Chem.Lett.* 1996; 2307; *Collect.Czech.Chem.Comm.* 1987; 52, 2095; *Synthesis* 2000, 1709) (1 mmol) was dissolved in a mixture of anhydrous acetonitrile and ethyl diisopropylamine (1 mmol). An acid chloride ClCOR<sup>15</sup> (1 mmol) was added at 0°C and the mixture was stirred at 0° for 60 min. The mixture was evaporated *in vacuo*, taken up in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate 25 ml, brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. The crude product was taken up in ethanol (50 ml), 5% palladium on charcoal (50 mg) was added and the mixture was hydrogenated for 24 h at 3 bar in a Parr hydrogenation apparatus. The mixture was filtrated and evaporated *in vacuo* to give the final piperidines.

**Example 12** Piperidines of formula III where Q is (iii), and R<sup>12</sup> is phenyl and R<sup>13</sup> is a group -NR<sup>16</sup>COCONR<sup>17</sup>R<sup>18</sup>

1-Benzyl-4-phenyl-piperidin-4-ylamine (*Bioorg.Med.Chem.Lett.* 1996; 2307; *Collect.Czech.Chem.Comm.* 1987; 52, 2095; *Synthesis* 2000, 1709) (1 mmol) was dissolved in a mixture of anhydrous acetonitrile and ethyl diisopropylamine (1 mmol). An acid chloride ClCOCONR<sup>17</sup>R<sup>18</sup> (1 mmol) was added at 0°C and the mixture was stirred at 0° for 60 min. The mixture was evaporated *in vacuo*, taken up in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate 25 ml, brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. The crude product was taken up in ethanol (50 ml), 5% palladium on charcoal (50 mg) was added and the mixture was hydrogenated for 24 h at 3 bar in a Parr hydrogenation apparatus. The mixture was filtrated and evaporated *in vacuo* to give the final piperidines.

**Example 13 Piperidines of formula III where Q is (iii), and R<sup>12</sup> is phenyl and R<sup>13</sup> is a group -NR<sup>22</sup>SO<sub>2</sub>R<sup>23</sup>**

1-Benzyl-4-phenyl-piperidin-4-ylamine (*Bioorg.Med.Chem.Lett.* 1996; 2307;

- 5 *Collect.Czech.Chem.Comm.* 1987; 52, 2095; *Synthesis* 2000, 1709) (1 mmol) was dissolved in a mixture of anhydrous acetonitrile and ethyl diisopropylamine (1 mmol). An sulphonyl chloride ClSO<sub>2</sub>R<sup>23</sup> (1 mmol) was added at 0°C and the mixture was stirred at 0° for 60 min. The mixture was evaporated *in vacuo*, taken up in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate 25 ml), brine (25 ml), dried over  
10 anhydrous magnesium sulphate and evaporated *in vacuo*. The crude product was taken up in ethanol (50 ml), 5% palladium on charcoal (50 mg) was added and the mixture was hydrogenated for 24 h at 3 bar in a Parr hydrogenation apparatus. The mixture was filtrated and evaporated *in vacuo* to give the final piperidines.

15 **Example 14 Preparation of the compounds of the invention**

The compounds of the present invention were prepared by one of two general methods:

**Method A: Alkylating a piperidine of formula III with an alkylating derivative of formula II:**

- 20 A suitable substituted (1S,2R)-2-hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid amide (1 mmol) was dissolved in dichloromethane (20 ml) and phosphorus tribromide (3 mmol) was added and the mixture stirred at rt for 3 h. Water (10 ml) was added and after stirring for 10 minutes the dichloromethane phase was isolated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to a clear oil which was used immediately  
25 without further purification by dissolving in anhydrous acetonitrile (10 ml) and added to a mixture of a piperidine of formula III (1 mmol), and ethyl diisopropyl amine (1.3 mmol) in acetonitrile (10 mL) and the mixture was heated to 85 °C for 3 h. The mixture was cooled to room temperature and evaporated *in vacuo*. The product was purified by chromatography either on silicagel using as eluent ethylacetate/triethylamine (99:1) or by purified by HPLC.  
30 Fractions containing the product were pooled and evaporated *in vacuo* and characterised by HPLC-UV-ELSD-MS. The measured HPLC-retention time, the measured molecular mass and UV- and ELSD-purities are shown in Table 1.

**Method B: Reacting an amine of formula VI with an acid of formula VIII by the use of an activating reagent or a coupling reagent:**

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl) cyclopropanecarboxylic acid hydrochloride (0.05 mmol) was dissolved in anhydrous DMF.

- 5 Ethyl diisopropylamine (0.15 mmol), benzylamine (0.075 mmol), dimethylaminopyridine (0.05 mmol) and BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate 0.1 mmol) were added and the mixture stirred at rt for 2 h. The reaction mixture was evaporated *in vacuo* and the product purified by HPLC. Fractions containing the product were pooled and evaporated *in vacuo* and characterised by HPLC-  
10 UV-ELSD-MS. The measured HPLC-retention time, the measured molecular mass and UV- and ELSD-purities are shown in table 1.

**The following compounds were made by the methods indicated in the table. Analytical data are shown in table 1.**

- 15 Table 1. Measured molecular mass, measured HPLC-retention time (RT, min) and UV- and ELSD-purities (%) and synthesis method.

compound	M+H <sup>+</sup>	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
1a	564,2	2,5	98.49	97.90	A
2a	578,5	2,7	41.8	99.2	A
3a	576,3	2,6	82.5	98.3	A
4a	594,3	2,6	98.17	98.59	A
5a	590,2	2,6	82.6	100	A
6a	608,5	2,8	96.65	99.48	A
7a	550,2	2,5	97.87	99.93	A
8a	544,2	2,4	82.38	99.91	A
9a	481,3	2,3	92.92	100	A
10a	557,1	2,6	75.95	99.33	A
12a	530,2	2,2	95.68	99.83	A
13a	584,3	2,5	97.25	99.47	A
14a	544,1	2,7	93.6	99.8	A

15a	515,2	2,4	72.36	99.83	A
16a	542,3	2,5	88.53	100	A
17a	560,3	2,4	98.21	99.95	A
18a	546,4	2,4	96.39	99.87	A
19a	560,3	2,3	90.62	100	A
20a	576,4	2,4	94.47	100	A
21a	514,2	2,4	99.42	99.84	A
22a	528,4	2,2	96.9	99.8	A
23a	526,4	2,3	75.77	99.95	A
24a	575,1	2,2	97.43	99.74	A
25a	544,3	2,6	90.09	99.48	A
26a	562	2,3	96.58	99.84	A
27a	604,4	2,4	95.66	100	A
28a	533,1	2,5	99.44	100	A
29a	560,1	2,5	98.16	99.81	A
30a	578,2	2,4	97.01	99.87	A
31a	586,2	2,4	97.17	100	A
32a	562,2	2,6	91.69	99.36	A
33a	604,4	2,3	93.68	99.44	A
34a	606,5	2,6	84.9	99.19	A
35a	580,4	2,4	96.74	98.84	A
36a	618,2	2,4	92.3	99.95	A
37a	549,2	2,8	100	99.34	A
38a	558,3	2,6	97.21	99.97	A
39a	578,3	2,4	99.62	98.43	A
40a	632,4	2,5	100	99.77	A
41a	592,2	2,9	99.11	98.91	A
42a	568,5	2,5	99.3	99.97	A
43a	602,3	2,5	87	99.68	A
44a	548,3	2,7	94.96	99.24	A
45a	564,1	2,5	96.864	98.061	A
46a	618,2	2,4	97.35	99.74	A

47a	580,4	2,8	93.59	98.34	A
48a	594,3	2,5	93.88	98.39	A
49a	562,2	2,5	98.65	99.69	A
50a	580,5	2,4	94.44	99.91	A
51a	598	2,4	92.14	99.97	A
52a	654,3	2,5	96.76	99.82	A
53a	614,1	2,8	92.98	98.17	A
54a	610,3	2,6	100	100	A
55a		2,6	99.79	99.89	B
56a		2,7	95.24	99.87	B
57a	614,1	2,79	100	99.96	A
58a	610,3	2,45	58.47	99.76	A
59a		2,51			A
60a		2,31			A
61a		2,31			A

### Example 15 Receptor binding assay

The binding assay is based on previously described methods (Chung FZ et al: Mol Pharmacol. 1995 48 p711-6 and Sarau HM et al: J Pharmacol Exp Ther. 1997 281 p1303-11).

#### Membrane preparation:

Membranes were isolated from baby hamster kidney (BHK) cells stably expressing the human NK1 or NK3 receptors or from Chinese hamster ovary (CHO) cells stably expressing the human NK2 receptor. 24 hours before harvesting, the BHK cells were treated with trichostatin A (TSA) to increase expression. The cells were washed twice with icecold phosphate-buffered saline without  $Mg^{2+}$ ,  $Ca^{2+}$  and Sodium bicarbonate (PBS). The cells were scraped in 10 ml PBS and centrifuged for 3 min at 4°C and 1500 g. The supernatant was discarded and the pellet was resuspended in 10 ml of 15 mM Tris-HCl pH 7,5 buffer containing 2 mM  $MgCl_2$ , 0,3 mM EDTA, 1 mM EGTA (buffer A) and subsequently Dounce homogenised. (For the NK1 receptor containing membranes an extra step with 5 min centrifugation at 4°C and 1500 g followed by resuspension of the pellet in 10 ml buffer A was included to enrich the membrane preparation). The suspension was centrifuged for 25 min at 4°C and 40000 g. The supernatant was discarded, the pellet was washed with 10 ml

buffer A and the suspension was centrifuged for 25 min at 4°C and 40000 g. The supernatant was discarded and the pellet was resuspended in 7,5 mM Tris-HCl pH 7,5 containing 12,5 mM MgCl<sub>2</sub>, 0,3 mM EDTA, 1 mM EGTA and 250 nM sucrose, frozen in liquid nitrogen and stored at -80 °C.

5

**Competition binding assay:**

For the NK3 binding assay, membranes were incubated with 0,1 nM <sup>125</sup>I-eledoisin in 50 mM Tris pH 7.4 buffer containing 3 mM MnCl<sub>2</sub>, 40µg/ml bacitracin, 2µg/ml chymostatin, 2µM phosphoramidon, 4µg/ml leupeptin, 0,02% bovine serum albumin (BSA) and selected concentrations of compounds for 60 min at 25 °C.

10

For the NK1 and NK2 binding assay, the membranes were incubated with 0,1 nM <sup>125</sup>I-substance P or 0,1 nM <sup>125</sup>I-NKA, respectively in 50 mM Tris pH 7.4 buffer containing 3 mM MnCl<sub>2</sub> and 0,02% BSA and selected concentrations of compounds for 60 min at 25 °C.

The assay was terminated by rapid filtration through GF/C UniFilters presoaked with 1% BSA (NK3 binding assay) or 0,1% polyethyleneimine (NK1 and NK2 binding assays) using a Tomtec harvester. The filters were washed 3 times with ice-cold 50 mM Tris pH 7,4, dried and added scintillant before counting in a Wallac scintillation counter.

15

For each compound, the IC<sub>50</sub> value (the concentration required to obtain 50% inhibition of the radioligand) was determined from concentration-response curves and used to calculate the K<sub>i</sub> from the equation  $K_i = IC_{50} / (1 + L / K_d)$ , where L is the concentration of radioligand. K<sub>d</sub> is the dissociation constant of the radioligand and was determined from saturation binding experiment.

20

The compounds 1a-56a all had a NK3 binding affinity (IC<sub>50</sub>) of less than 50 nM. The compounds 57a-61a all had a NK3 binding affinity (IC<sub>50</sub>) of less than 1000 nM.

25

**Example 16 The Fluorometric Imaging Plate Reader (FLIPR) assay:**

The compounds were analysed for efficacy profile in FLIPR assays similar to assays described in Jerman, JC et al: Eur J Pharmacol. 2001, 414, p23-30. BHK cells (cf. Example 15) stably expressing the human NK3 receptor were seeded in 100 µl media in black walled clear-base 96-wells plates (Costar) aiming at a confluency of 95-100% at the day of assay. The assay was performed according to the calcium assay kit (Molecular Devices). Briefly, the calcium assay reagent was dissolved in Hanks BSS (HBSS) buffer, pH 7,4 containing 20

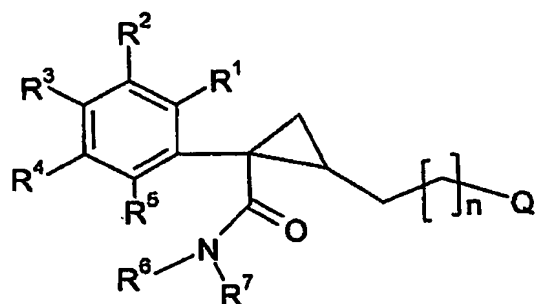
30

mM Hepes and 2,5 mM probenidol. An equal volume (100  $\mu$ l) of the calcium assay reagent solution was added to the wells and the plates were incubated for 60 min at 37°C. The plates were subsequently placed in the FLIPR for examination of fluorescence.

Compounds were diluted in HBSS buffer containing 20 mM Hepes prior to test. For test of  
5 agonist activity 50  $\mu$ l of compound was added to the wells and the plates were analysed for  
3 minutes in the FLIPR. For test of antagonist activity, 25  $\mu$ l of compound was added to the  
wells and the plate was analysed for a 5 minute period. Subsequently, the wells were added  
25  $\mu$ l of an EC<sub>85</sub> concentration of NKB (app. 1 nM) previously determined from a dose-  
response curve with NKB. The plates were subsequently read for 3 minutes before  
10 termination. As controls, selected wells on all plates were added only 100 nM of the NK3  
receptor agonist NKB or 2  $\mu$ M of the calcium ionophor ionomycin. The maximal increase in  
fluorescence over background following each ligand addition was determined and analysed.

## CLAIMS

1. A compound of formula I

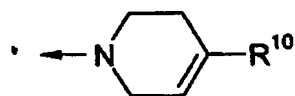


(I)

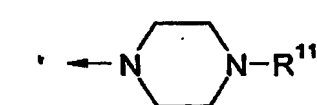
or a salt thereof, such as a pharmaceutically acceptable salt;  
wherein

- $R^1$ - $R^5$  are independently selected from hydrogen, halogen, cyano, nitro,  $C_{1-6}$ -alk(en/yn)yl,  $C_{3-8}$ -cycloalk(en)yl,  $C_{3-8}$ -cycloalk(en)yl- $C_{1-6}$ -alk(en/yn)yl, amino,  $C_{1-6}$ -alk(en/yn)ylamino, di- $(C_{1-6}$ -alk(en/yn)yl)amino,  $C_{1-6}$ -alk(en/yn)ylcarbonyl, aminocarbonyl,  $C_{1-6}$ -alk(en/yn)ylaminocarbonyl, di- $(C_{1-6}$ -alk(en)yl)aminocarbonyl, hydroxy,  $C_{1-6}$ -alk(en/yn)ylloxy,  $C_{1-6}$ -alk(en/yn)ylthio, halo- $C_{1-6}$ -alk(en/yn)yl, halo- $C_{1-6}$ -alk(en/yn)ylsulfonyl, halo- $C_{1-6}$ -alk(en/yn)ylsulfanyl, and  $C_{1-6}$ -alk(en/yn)ylsulfonyl;
- $R^6$  is selected from hydrogen, halo- $C_{1-6}$ -alk(en/yn)yl,  $C_{1-6}$ -alk(en/yn)yl,  $C_{3-8}$ -cycloalk(en)yl, and  $C_{3-8}$ -cycloalk(en)yl- $C_{1-6}$ -alk(en/yn)yl ;
- $R^7$  is an aryl or a heteroaryl; or  $R^7$  is a group aryl- $CR^8R^9$ -, wherein  $R^8$  and  $R^9$  is independently selected from hydrogen,  $C_{1-6}$ -alk(en/yn)yl,  $C_{3-8}$ -cycloalk(en)yl, and  $C_{3-8}$ -cycloalk(en)yl- $C_{1-6}$ -alk(en/yn)yl;
- $n$  is 0, 1, or 2;

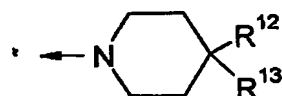
Q is selected from (i)-(vii), the arrow indicating the attachment point:



(i)

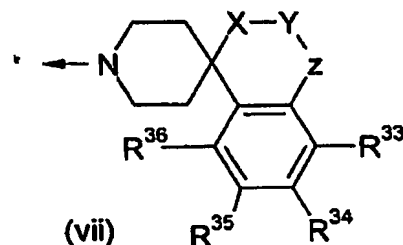
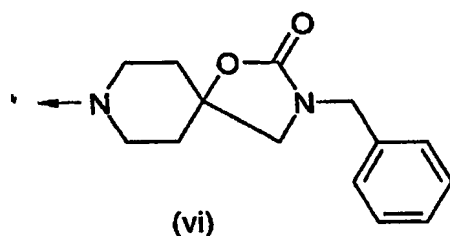
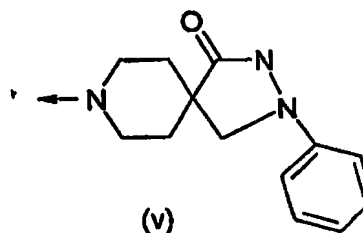
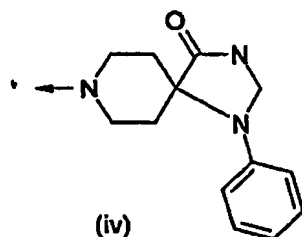


(ii)



(iii)





wherein  $R^{10}$  is an aryl;

wherein  $R^{11}$  is selected from an aryl or benzyl, halo- $C_{1-6}$ -alk(en/yn)ylsulfonyl,  $C_{1-6}$ -alk(en/yn)ylsulfonyl, arylsulphonyl, arylacyl,  $C_{1-6}$ -alk(en/yn)ylcarbonyl, aminocarbonyl,  $C_{1-6}$ -alk(en/yn)ylaminocarbonyl, and di- $(C_{1-6}$ -alk(en)yl)aminocarbonyl;

wherein  $R^{12}$  is an aryl;

wherein  $R^{13}$  is hydrogen, hydroxy, cyano, or amino, or one of the following groups:

- $NHC_{1-6}$ -alk(en/yn)yl;

- $N(C_{1-6}$ -alk(en/yn)yl)<sub>2</sub>;

- $NR^{14}COR^{15}$ , wherein  $R^{14}$  is hydrogen or  $C_{1-6}$ -alk(en/yn)yl and  $R^{15}$  is  $C_{1-6}$ -alk(en/yn)yl or  $C_{3-8}$ -cycloalk(en)yl;

- $NR^{16}COCONR^{17}R^{18}$ , wherein  $R^{16}$  is hydrogen or  $C_{1-6}$ -alk(en/yn)yl and  $R^{17}$  and  $R^{18}$

are selected independently from hydrogen,  $C_{1-6}$ -alk(en/yn)yl and  $C_{3-8}$ -cycloalkyl; or  $R^{17}$  and  $R^{18}$  together with the nitrogen to which they are attached

form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $C_{1-6}$ -alk(en/yn)yl;

- $NR^{19}CONR^{20}R^{21}$ , wherein  $R^{19}$  is hydrogen or  $C_{1-6}$ -alk(en/yn)yl and  $R^{20}$  and  $R^{21}$  are

selected independently from hydrogen and  $C_{1-6}$ -alk(en/yn)yl or  $C_{3-8}$ -cycloalkyl;

or  $R^{20}$  and  $R^{21}$  together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $C_{1-6}$ -alk(en/yn)yl;

-NR<sup>22</sup>SO<sub>2</sub>R<sup>23</sup>, wherein R<sup>22</sup> is hydrogen, C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl and R<sup>23</sup> is amino, C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl;

-COR<sup>24</sup>, wherein R<sup>24</sup> is C<sub>1-6</sub>-alk(en/yn)yl or C<sub>3-8</sub>-cycloalkyl;

-CONR<sup>25</sup>R<sup>26</sup>, wherein R<sup>25</sup> and R<sup>26</sup> independently are selected from hydrogen, C<sub>1-6</sub>-alk(en/yn)yl and C<sub>3-8</sub>-cycloalkyl; or R<sup>25</sup> and R<sup>26</sup> together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a C<sub>1-6</sub>-alkyl;

wherein X, Y, and Z are selected independently from a bond; O; NR<sup>27</sup>; CR<sup>28</sup>R<sup>29</sup> and S(O)<sub>m</sub>, wherein m is 0, 1 or 2;

wherein R<sup>27</sup> is selected from hydrogen, C<sub>1-6</sub>-alk(en/yn)yl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl; or

R<sup>27</sup> is a group R<sup>30</sup>SO<sub>2</sub>-, R<sup>30</sup>OCO- or R<sup>30</sup>SCO-, wherein R<sup>30</sup> is C<sub>1-6</sub>-alk(en/yn)yl, C<sub>3-8</sub>-cycloalkyl, or C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl; or

R<sup>27</sup> is a group R<sup>31</sup>R<sup>32</sup>NCO- or R<sup>31</sup>R<sup>32</sup>NCS-, wherein R<sup>31</sup> and R<sup>32</sup> are independently selected from hydrogen, C<sub>1-6</sub>-alk(en/yn)yl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl and aryl; or wherein R<sup>31</sup> and R<sup>32</sup> together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group;

wherein R<sup>28</sup> and R<sup>29</sup> are independently selected from hydrogen, fluoro, C<sub>1-6</sub>-alk(en/yn)yl, C<sub>3-8</sub>-cycloalkyl, and C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl;

wherein R<sup>33</sup>-R<sup>36</sup> are independently selected from hydrogen, halogen, cyano, nitro, C<sub>1-6</sub>-alk(en/yn)yl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-alkyl, amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)amino, C<sub>1-6</sub>-alkylcarbonyl, aminocarbonyl, C<sub>1-6</sub>-alkylaminocarbonyl, di-(C<sub>1-6</sub>-alkyl)aminocarbonyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C<sub>1-6</sub>-alkylsulfonyl;

provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S.

2. The compound or salt of claim 1, wherein R<sup>1</sup>-R<sup>5</sup> are independently selected from hydrogen, halogen, cyano, C<sub>1-6</sub>-alk(en/yn)yl, C<sub>3-8</sub>-cycloalk(en)yl, C<sub>3-8</sub>-cycloalk(en)yl-C<sub>1-6</sub>-alk(en/yn)yl, C<sub>1-6</sub>-alk(en/yn)yl, C<sub>1-6</sub>-alk(en/yn)ylthio, and halo-C<sub>1-6</sub>-alkyl, .e.g trifluoromethyl.

3. The compound or salt of claim 1, wherein R<sup>1</sup>-R<sup>5</sup> is Hydrogen.

4. The compound or salt of claim 1, wherein  $R^1$ - $R^5$  are independently selected from hydrogen and halogen.
5. The compound or salt of claim 1, wherein  $R^1$ - $R^5$  are independently selected from hydrogen and chloro.
- 5 6. The compound or salt of claim 1, wherein  $R^1$ - $R^5$  are independently selected from hydrogen and fluoro.
7. The compound or salt of claim 5, wherein  $R^2$  is chloro and  $R^3$  is hydrogen.
8. The compound or salt of claim 5, wherein  $R^2$  and  $R^3$  is chloro.
9. The compound or salt of claim 6, wherein  $R^2$  is fluoro and  $R^3$  is hydrogen.
- 10 10. The compound or salt of claim 6, wherein  $R^2$  and  $R^3$  is fluoro.
11. The compound or salt of any of claims 7-10, wherein  $R^1$ ,  $R^4$  and  $R^5$  is hydrogen.
12. The compound or salt of any of claims 1-11, wherein  $R^6$  is selected from hydrogen,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, and  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl.
- 13 The compound or salt of any of claims 1-11, wherein  $R^6$  is selected from hydrogen  
15 and  $C_{1-6}$ -alk(en/yn)yl.
14. The compound or salt of any of claims 1-11, wherein  $R^6$  is hydrogen.
15. The compound or salt of of any of claims 1-11, wherein  $R^6$  is a  $C_{1-6}$ -alkyl.
16. The compound or salt of claim 15, wherein  $R^6$  is methyl.
17. The compound or salt of any of claims 1-16, wherein  $R^7$  is the group aryl- $CR^8R^9$ .
- 20 18. The compound or salt of claim 17, wherein  $R^8$  and  $R^9$  are independently selected from hydrogen,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl and  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl.
19. The compound or salt of claim 17, wherein  $R^8$  and  $R^9$  are independently selected from hydrogen and  $C_{1-6}$ -alkyl.
20. The compound or salt of claim 17, wherein  $R^8$  and  $R^9$  are independently selected  
25 from hydrogen and methyl.
21. The compound or salt of claim 17, wherein  $R^8$  and  $R^9$  is hydrogen.
22. The compound or salt of claim 17, wherein  $R^8$  is hydrogen and  $R^9$  is methyl.
23. The compound of any of claims 1-16, wherein  $R^7$  as an aryl or a heteroaryl.
24. The compound or salt of any of claims 17-23, wherein said aryl or heteroaryl is  
30 monocyclic or bicyclic.
25. The compound or salt of any of claims 17-24, wherein said aryl or heteroaryl is unsubstituted.

26. The compound or salt of any of claims 17-24, wherein said aryl or heteroaryl is substituted with one or more substituents.
27. The compound or salt of claim 26, wherein said aryl or heteroaryl is substituted with one or more substituents selected from halogen, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>2-6</sub>-alkynyl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)amino, C<sub>1-6</sub>-alkylcarbonyl, aminocarbonyl, C<sub>1-6</sub>-alkylaminocarbonyl, di-(C<sub>1-6</sub>-alkyl)aminocarbonyl, C<sub>1-6</sub>-alkylcarbonylamino, C<sub>1-6</sub>-alkylcarbonyl C<sub>1-6</sub>-alkylamino, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkylthio, hydroxy, trifluoromethyl, difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.
- 10 28. The compound or salt of any of claims 24-27, wherein R<sup>7</sup> is the group aryl-CR<sup>8</sup>R<sup>9</sup>- as defined in any of claims 17-22, and the aryl of said group aryl-CR<sup>8</sup>R<sup>9</sup>- is as defined in any of claims 24-27.
29. The compound or salt of claim 28, wherein said aryl is an optionally substituted phenyl.
- 15 30. The compound or salt of claim 28 or 29, wherein said aryl is mono- or poly-substituted, including di-substituted, with a halogen, e.g. fluoro or chloro.
31. The compound of claim 17, wherein R<sup>7</sup> is the group aryl-CR<sup>8</sup>R<sup>9</sup>- and R<sup>7</sup> is selected from benzyl, or halogen substituted benzyl, e.g. 4-halo benzyl, such as 4-fluorobenzyl, or 2-halo-benzyl, such as 2-chloro-benzyl.
- 20 32. The compound or salt of any of claims 1-31, wherein Q is (i).
33. The compound or salt of claim 32, wherein R<sup>10</sup> is an aryl as defined in any of claims 24-30.
34. The compound or salt of any of claims 1-31, wherein Q is (ii).
35. The compound or salt of claim 34, wherein R<sup>11</sup> is selected from an optionally substituted aryl or optionally substituted benzyl, trifluoromethylsulfonyl, C<sub>1-6</sub>-alkylsulfonyl, arylsulphonyl, arylacyl, C<sub>1-6</sub>-alkylcarbonyl, aminocarbonyl, C<sub>1-6</sub>-alkylaminocarbonyl and di-(C<sub>1-6</sub>-alkyl)aminocarbonyl).
- 25 36. The compound or salt of claim 34 or 35, wherein R<sup>11</sup> is an aryl as defined in any of claims 24-30.
- 30 37. The compound or salt of claim 34, wherein R<sup>11</sup> is an arylsulphonyl or an arylcarbonyl, wherein the aryl part of said arylsulphonyl or arylacyl is as defined in any of claims 24-30.
38. The compound or salt of any of claims 1-31, wherein Q is selected from (iii-vii).

39. The compound or salt of claim 38, wherein Q is (iii).
40. The compound or salt of claim 39, wherein  $R^{12}$  is an aryl as defined in any of claims 24-30.
41. The compound or salt of claim 39, wherein  $R^{12}$  is a phenyl.
- 5 42. The compound or salt of claim 39, wherein  $R^{12}$  is a phenyl substituted with one or more substituents.
43. The compound or salt of claim 40 or 42, wherein said aryl in  $R^{12}$  is substituted with one or more substituents selected from a halogen and trifluoromethyl.
44. The compound or salt of claim 39, wherein  $R^{12}$  is 4-chloro-3-trifluoromethyl-phenyl.
- 10 45. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is selected from hydroxy,  $-NR^{14}COR^{15}$ ,  $-NR^{16}COCONR^{17}R^{18}$ ,  $-NR^{19}CONR^{20}R^{21}$ ,  $-NR^{22}SO_2R^{23}$ ,  $-COR^{24}$ , and  $-CONR^{25}R^{26}$ .
46. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is hydroxy.
47. The compound or salt of claim 46, wherein  $R^{12}$  is as defined in claim 44.
- 15 48. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is  $-NR^{14}COR^{15}$ .
49. The compound or salt of claim 48, wherein  $R^{14}$  is hydrogen or  $C_{1-6}$ -alkyl and  $R^{15}$  is  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl.
50. The compound or salt of claim 48 or 49, wherein  $R^{14}$  is hydrogen or methyl.
51. The compound or salt of any of claims 48-50, wherein  $R^{15}$  is methyl.
- 20 52. The compound or salt of claim 48, wherein  $R^{14}$  is hydrogen and  $R^{15}$  is methyl; or  $R^{14}$  and  $R^{15}$  is methyl.
53. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is  $-NR^{16}COCONR^{17}R^{18}$ .
54. The compound or salt of claim 53, wherein  $R^{16}$  is hydrogen or  $C_{1-6}$ -alkyl and wherein  $R^{17}$  and  $R^{18}$  are selected independently from hydrogen,  $C_{1-6}$ -alkyl and  $C_{3-8}$ -cycloalkyl.
- 25 55. The compound or salt of claim 53, wherein  $R^{16}$  is hydrogen or  $C_{1-6}$ -alkyl and wherein  $R^{17}$  and  $R^{18}$  together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $C_{1-6}$ -alkyl.
- 30 56. The compound or salt of claim 53, wherein said  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are hydrogen;  $R^{16}$  is  $C_{1-6}$ -alkyl, and  $R^{17}$  and  $R^{18}$  are hydrogen;  $R^{16}$  and  $R^{17}$  are hydrogen and  $R^{18}$  is  $C_{1-6}$ -alkyl;  $R^{16}$  and  $R^{17}$  are  $C_{1-6}$ -alkyl and  $R^{18}$  is hydrogen;  $R^{16}$  is hydrogen and  $R^{17}$  and  $R^{18}$  are  $C_{1-6}$ -alkyl; or  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  is  $C_{1-6}$ -alkyl.

57. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is  $-NR^{19}CONR^{20}R^{21}$ .
58. The compound or salt of claim 57, wherein  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are independently selected from hydrogen,  $C_{1-6}$ -alkyl and  $C_{3-8}$ -cycloalkyl.
59. The compound or salt of claim 57, wherein  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are independently  
5 selected from hydrogen and  $C_{1-6}$ -alkyl.
60. The compound or salt of claim 57, wherein  $R^{19}$  is a  $C_{1-6}$ -alkyl and  $R^{20}$  and  $R^{21}$  are hydrogen;  $R^{19}$  and  $R^{20}$  are hydrogen and  $R^{21}$  is a  $C_{1-6}$ -alkyl;  $R^{19}$  and  $R^{20}$  is independently selected from a  $C_{1-6}$ -alkyl and  $R^{21}$  is H;  $R^{19}$  is H, and  $R^{20}$  and  $R^{21}$  is independently selected from a  $C_{1-6}$ -alkyl; or  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  is independently selected from a  $C_{1-6}$ -alkyl.
- 10 61. The compound or salt of claim 59, wherein  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are hydrogen.
62. The compound or salt of any of claims 57-60, wherein  $R^{19}$  is H.
63. The compound or salt of any of claims 57-60, wherein  $R^{20}$  and  $R^{21}$  is independently selected from the group consisting of hydrogen, Me, Et, Bu, and i-Pr.
64. The compound or salt of claim 63, wherein  $R^{19}$  is H.
- 15 65. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is  $-NR^{22}SO_2R^{23}$ .
66. The compound or salt of claim 65, wherein  $R^{22}$  is hydrogen, a  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl and  $R^{23}$  is amino,  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl.
67. The compound or salt of claim 65 or 66, wherein  $R^{22}$  is hydrogen and  $R^{23}$  is a  $C_{1-6}$ -alkyl or  $R^{22}$  and  $R^{23}$  are independently selected from a  $C_{1-6}$ -alkyl.
- 20 68. The compound or salt of any of claims 65-66, wherein  $R^{22}$  is hydrogen.
69. The compound or salt of any of claims 65-68, wherein  $R^{23}$  is methyl.
70. The compound or salt of any of claims 65-67, wherein  $R^{22}$  and  $R^{23}$  is methyl.
71. The compound or salt of any of claims 65-67, wherein  $R^{22}$  is hydrogen and  $R^{23}$  is methyl.
- 25 72. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is  $-COR^{24}$ .
73. The compound or salt of claim 72, wherein  $R^{24}$  is a  $C_{1-6}$ -alkyl.
74. The compound or salt of claim 72, wherein  $R^{24}$  is methyl.
75. The compound or salt of any of claims 39-44, wherein  $R^{13}$  is  $-CONR^{25}R^{26}$ .
76. The compound or salt of claim 75, wherein  $R^{25}$  and  $R^{26}$  are independently selected  
30 from hydrogen,  $C_{1-6}$ -alkyl and  $C_{3-8}$ -cycloalkyl.
77. The compound or salt of claim 75, wherein  $R^{25}$  and  $R^{26}$  are independently selected from hydrogen and methyl.

78. The compound or salt of claim 75, wherein  $R^{25}$  and  $R^{26}$  together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a  $C_{1-6}$ -alkyl.

5 79. The compound or salt of claim 75, wherein  $R^{25}$  and  $R^{26}$  together with the nitrogen to which they are attached form a piperidinyl, wherein said piperidinyl is optionally substituted with a  $C_{1-6}$ -alkyl.

80. The compound or salt of any of claims 1-31, wherein Q is (vii).

81. The compound or salt of claim 80, wherein Y is a bond and X and Z are selected independently from O;  $NR^{27}$ ; and  $CR^{28}R^{29}$  and  $S(O)_m$ , provided that X and Z may not at the  
10 same time be selected from O and S.

82. The compound or salt of claim 80, wherein Y is a bond and said X and Z are selected independently from  $CR^{28}R^{29}$  and  $NR^{27}$ .

83. The compound or salt of claim 80, wherein X is  $CR^{28}R^{29}$ , Y is a bond and Z is  $NR^{27}$ .

84. The compound or salt of claim 83, wherein  $R^{28}$  and  $R^{29}$  are hydrogen.

15 85. The compound or salt of claim 81, wherein X is  $CR^{28}R^{29}$  and said  $R^{28}$  and  $R^{29}$  are hydrogen.

86. The compound or salt of any of claims 80, wherein X is  $CR^{28}R^{29}$ , Y is a bond and Z is O.

87. The compound or salt of claim 86, wherein  $R^{28}$  and  $R^{29}$  are hydrogen.

20 88. The compound or salt of claim 80, wherein X is O, Y is a bond and Z is  $CR^{28}R^{29}$ .

89. The compound or salt of claim 88, wherein  $R^{28}$  and  $R^{29}$  are hydrogen.

90. The compound or salt of any of claims 80-89, wherein said  $R^{27}$  is an acyl.

91. The compound or salt of claim 90, wherein said  $R^{27}$  is a  $C_{1-6}$ -alkylcarbonyl.

25 92. The compound or salt of claim 83, wherein Z is  $NR^{27}$  and said  $R^{27}$  is a  $C_{1-6}$ -alkylcarbonyl.

93. The compound or salt of claim 92, wherein said  $R^{27}$  is  $-COCH_3$ .

94. The compound or salt of any of claims 83, wherein X is  $CR^{28}R^{29}$ , said  $R^{28}$  and  $R^{29}$  are hydrogen; Y is a bond; and Z is  $-NR^{27}$ , said  $R^{27}$  is  $-COCH_3$ .

95. The compound or salt of any of claims 80-89, wherein said  $R^{27}$  is selected from the  
30 group  $R^{30}SO_2-$ ,  $R^{30}OCO-$  and  $R^{30}SCO-$ .

96. The compound or salt of any of claims 80-89, wherein  $R^{27}$  is  $R^{30}SO_2$ .

97. The compound or salt of claim 96, wherein  $R^{30}$  is  $C_{1-6}$ -alkyl.

98. The compound or salt of claim 96, wherein  $R^{30}$  is methyl.

99. The compound or salt of any of claims 96-98, wherein X is  $\text{CR}^{28}\text{R}^{29}$ , Y is a bond and Z is  $\text{NR}^{27}$ .

100. The compound or salt of claim 99, wherein  $\text{R}^{28}$  and  $\text{R}^{29}$  is hydrogen.

101. The compound or salt of any of claims 80-89, wherein  $\text{R}^{27}$  is the group  $\text{R}^{31}\text{R}^{32}\text{NCO-}$  or  $\text{R}^{30}\text{R}^{31}\text{NCS-}$ .

102. The compound or salt of any of claims 80-102, wherein at Y is a bond.

103. The compound or salt of any of claims 80-102, wherein  $\text{R}^{33}\text{-R}^{36}$  are independently selected from hydrogen and halogen.

104. The compound or salt of of claim 1, wherein  $\text{R}^{1-5}$  is as defined in any of claims 3-11, and  $\text{R}^6$  is as defined in claim 13.

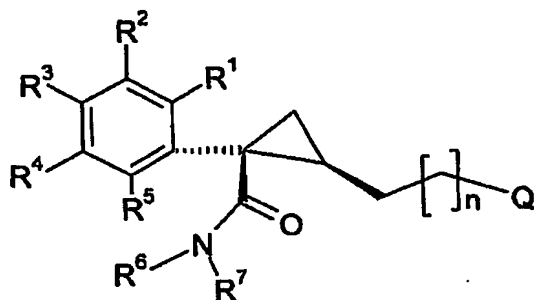
105. The compound or salt of of claim 1, wherein  $\text{R}^{1-5}$  is as defined in any of claims 3-11, and  $\text{R}^6$  is as defined in claim 15, e.g.  $\text{R}^6$  is methyl.

106. The compound or salt of claim 1, wherein  $\text{R}^6$  is as defined in claim 14 or 15, e.g.  $\text{R}^6$  is methyl and  $\text{R}^7$  is as defined in claim 31.

107. The compound or salt of any of claims 102-106, wherein Q is (iii) and said  $\text{R}^{12}$  is as defined in claim 41.

108. The compound or salt of any of claims 1-107, wherein  $n=0$ .

109. The compound of or salt of any of the preceding claims, wherein the compound of formula I is the (1S,2R)-isomer, i.e. said compound with absolute configuration as shown in formula IA.



(IA)

110. The compound or salt of any of claims 1-109, wherein the compound of formula I is a racemic mixtures comprising the (1S,2R)-isomer i.e. said compound with absolute configuration as shown in formula IA, said compound with the stereochemistry as shown in formula IA.



111. The compound or salt of any of claims 1-108, wherein the compound of formula I is a mixture of stereoisomers of said compound, which mixture comprises the (1S,2R)-isomer as defined in claim 109.

112. The compound or salt of claim 1 selected from:

- 5 (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-  
10 (3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;  
15 (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;  
(1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;  
20 (1S,2R)-2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-  
25 phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;  
30 (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;  
(1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

(1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-  
cyclopropanecarboxylic acid benzyl-methyl-amide;

(1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-  
chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

5 (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-  
methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluoro-phenyl)-  
cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

10 (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-  
phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-  
methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-  
ethyl) amide;

15 (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-  
cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-phenyl-  
cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-  
phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

20 (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-  
phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-  
methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

25 (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-  
phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-  
bicyclo[3.2.1]octane-8'-yl)]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-  
benzyl)-methyl-amide;

30 (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-  
cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-  
chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-1-(3,4-Difluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid -methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

(1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

(1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

(1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

(1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

(1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

5 (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

(1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

10 (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;

(1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

15 (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

(1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

20 (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

(1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;

25 (1S,2R)-1-(3,4-Dichloro-phenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide;

(1S,2R)-2-(4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-ethyl-amide;

30 (1S,2R)-2-(4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide -([R]-1-phenyl-ethyl) amide;

(1R,2S)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

(1R,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and

(1S,2S)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide.

5 113. A pharmaceutical composition comprising a compound as defined in any of claims 1-112.

114. Use of a compound as defined in any of claims 1-112 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of: schizophrenia, depression, anxiety, Parkinson's  
10 disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema, plasma extravasation and obesity.

115. Use of a compound as defined in any of claims 1-112 or a salt thereof for the  
15 preparation of a medicament for treatment of schizophrenia.

116. Use according to claim 115 for treatment of the positives symptoms of schizophrenia.

117. Use of a compound as defined in any of claims 1-112 or a salt thereof for the manufacture of a pharmaceutical preparation for treatment of a disorder in the central  
20 nervous system.

118. A method for the treatment of diseases selected from the group consisting of: schizophrenia, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and  
25 electrolyte homeostasis, ischemia, oedema, plasma extravasation and obesity, comprising administering a therapeutically effective amount of a compound as defined in any of claims 1-112 or a pharmaceutically acceptable salt thereof.

119. The method of the preceding claim, wherein the disease is schizophrenia.

6 120. A method for treatment of a disorder in the central nervous system comprising  
30 administering a therapeutically effective amount of a compound as defined in any of claims 1-112 or a salt thereof.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**